

HANNAMAN  
WALKLEY  
CROSS

MedStudy®

IM

FIFTEENTH EDITION **2013/2014**

# 15

## INTERNAL MEDICINE REVIEW CORE CURRICULUM

BOOK **1**

GASTROENTEROLOGY

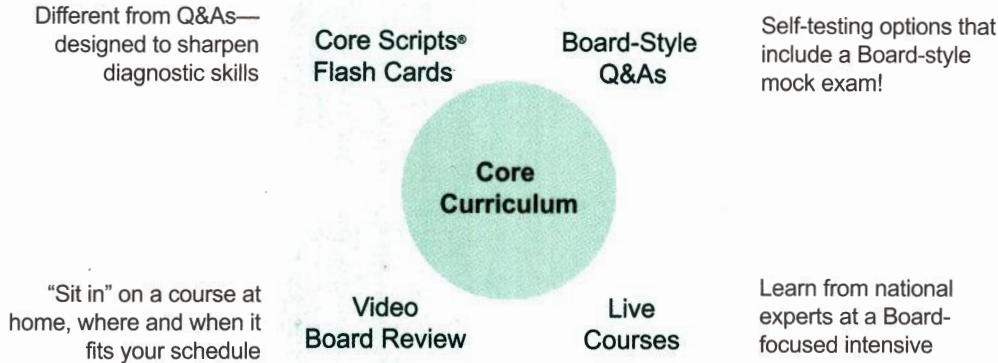


INFECTIOUS DISEASE



# MedStudy's flexible, synergistic Board-prep learning system.

Build on the Core Curriculum for a study/review combination that's right for you!



**Individually they're great. Together they're fantastic!**

Each component of our synergistic, Board-prep system complements the Core Curriculum, providing unique benefits for a well-rounded study/review program that fits your needs. You choose the resources that meet your budget, your study style, and your schedule.

## How the Core Curriculum works for you

### Must-know highlights:

Fundamental IM facts highlighted in yellow for exam prep at a glance.

### Key facts in accent type:

Essential terms and phrases accented in burgundy type, alerting you to key facts.

### Quick Quizzes:

Short questions appear on every 2-page spread so you can self-test as you go.

### Medical images:

Illustrated throughout with actual scans, x-rays, scopes, and photos for real-life visual clarification.

### Tables, charts, illustrations:

Extensive information condensed into easy-to-review format.

NEUMOTHORAX

Table 3-1 The Pneumothorax Differential

| Demographic Factors | Findings                              | Points Assigned |
|---------------------|---------------------------------------|-----------------|
| Demographic Factors | Males                                 | +10             |
|                     | Smoking                               | +10             |
|                     | Neoplastic disease                    | +10             |
|                     | Liver disease                         | +10             |
|                     | Congestive heart failure              | +10             |
| Comorbid Illnesses  | Cardiovascular disease                | +10             |
|                     | Renal disease                         | +10             |
|                     | Altered mental status                 | +10             |
|                     | Respiratory rate > 20 breaths/min     | +10             |
|                     | Systolic BP < 90 mmHg                 | +10             |
| Physical Exam       | Temp < 36°C or > 38°C                 | +10             |
|                     | Pulse > 120 bpm                       | +10             |
|                     | pH < 7.35                             | +10             |
|                     | BUN > 10.7 mmol/L                     | +10             |
|                     | Na < 130                              | +10             |
| Laboratory          | Glucose > 139                         | +10             |
|                     | Hct < 30%                             | +10             |
|                     | Hct > 60 mmHg or PO <sub>2</sub> < 60 | +10             |
|                     | Arterial effusion                     | +10             |
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|                     | Hct > 60 mmHg or PO <sub>2</sub> < 60 | +10             |
|                     | Arterial effusion                     | +10             |
| Laboratory          | pH < 7.35                             | +10             |
|                     | BUN > 10.7 mmol/L                     | +10             |
|                     | Na < 130                              | +10             |
|                     | Glucose > 139                         | +10             |
|                     | Hct < 30%                             | +10             |
| Laboratory          | Hct > 60 mmHg or PO <sub>2</sub> < 60 | +10             |
|                     | Arterial effusion                     | +10             |
|                     | pH < 7.35                             | +10             |
|                     |                                       |                 |



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INTERNAL MEDICINE REVIEW

# CORE CURRICULUM

15<sup>th</sup> EDITION

Book 1 of 5

Topics in this volume:

**Gastroenterology**

**Infectious Disease**

Robert A. Hannaman, MD  
with Candace L. Walkley, MD and J. Thomas Cross, Jr., MD, MPH, FACP

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INTERNAL MEDICINE REVIEW



**CORE CURRICULUM**

15<sup>th</sup> EDITION

Robert A. Hannaman, MD  
with J. Thomas Cross, Jr., MD, MPH, FACP

# GASTROENTEROLOGY

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# Gastroenterology

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## GI PROCEDURES

Contraindications to GI endoscopy include a recent MI, combative patient, and intestinal perforation.

Esophagogastroduodenoscopy (EGD) is the procedure of choice for:

- Evaluation of painful swallowing (odynophagia)
- Determining presence of a peptic ulcer—either instead of upper gastrointestinal (UGI) series or when the UGI is equivocal or negative—and always before peptic ulcer disease (PUD) surgery
- Workup of gastroesophageal reflux disease (GERD) if initial treatment fails, or if there are alarm signals (see GERD on [page 1-6](#))
- UGI bleed workup
- Workup of GI disease during pregnancy
- Dysphagia (**after** the barium swallow!)
- Prn for evaluation of an ingested foreign body
- Persistent dyspepsia (A normal EGD is necessary for diagnosis of non-ulcer dyspepsia.)

Endoscopic retrograde cholangiopancreatography (ERCP): 60% have an elevated amylase after ERCP, and acute pancreatitis occurs in 5–20%. Treat patients with possible bile duct obstruction with antibiotics before ERCP. Indications for ERCP are unclear, but it is often used to:

- Find an otherwise undetectable common duct stone
- Determine the cause of pancreatic duct obstruction
- Potentially diagnose chronic pancreatitis
- Rule out primary sclerosing cholangitis (PSC)—but magnetic resonance cholangiopancreatography (MRCP) is better
- Treat choledocholithiasis with cholangitis

ERCP is **contraindicated** in **acute** pancreatitis, except in the following conditions:

- Impacted gallstones
- Ascending cholangitis (bacterial infection causing cholangitis)

MRCP can be used to:

- Diagnose chronic pancreatitis
- Assess the lack of clinical improvement in acute pancreatitis
- Test of choice for primary sclerosing cholangitis (PSC)

Retrograde cholangiography visualizes the bile tract. (Percutaneous transhepatic cholangiography [PTC], U/S, CT scan, and HIDA scans are also used.) Retrograde pancreatography is used to visualize the pancreatic duct. Colonoscopy is discussed later.

Endoscopic ultrasonography (EUS) is done via a high-frequency ultrasound probe that is passed through the biopsy channel of the endoscope—allowing for exact placement. EUS is used especially in evaluating pancreatic diseases. EUS is also used in biliary duct disease, when an ERCP would normally be used, but is contraindicated (e.g., gallstone pancreatitis and pregnancy), or to confirm MRCP findings.

## ESOPHAGUS

### DYSPHAGIA

The initial act of normal swallowing (deglutition) is a voluntary action that leads to involuntary upper esophageal sphincter (UES) relaxation and epiglottis closure. The smooth muscle in the esophageal body then generates a peristaltic contraction, propelling the food bolus distally. The lower esophageal sphincter (LES) relaxes to allow the bolus to enter the gastric fundus.

Swallowing that does not proceed appropriately for any reason is termed **dysphagia**. The history often gives important clues as to the etiology of dysphagia. Distinguish dysphagia from **odynophagia**, where the patient perceives pain when the food bolus traverses the esophagus.

The causes of dysphagia can be categorized into 3 types:

- 1) **Transfer** disorders: This is due to neurologic deficit, resulting in difficulty transferring food from the mouth to the esophagus and leading to oropharyngeal muscle dysfunction. Symptoms include coughing, gagging, and nasal regurgitating immediately upon swallowing. Especially consider stroke and amyotrophic lateral sclerosis (ALS).
- 2) **Anatomic** or **structural** disorders: This is due to an actual physical obstruction of the esophageal lumen.
- 3) **Motility** disorders: trouble with transporting food from the upper esophagus to the stomach. This can be a failure of effective peristalsis and/or failure of LES relaxation. These disorders have endogenous or exogenous causes.

See [Table 1-1](#) and [Figure 1-1](#).

Diagnosis: Always work up dysphagia. Do **not** use empiric treatment.

- 1) The **barium swallow** is usually the 1<sup>st</sup> test performed in the workup of dysphagia, unless the etiology is known from past evaluations. It is definitely done as the 1<sup>st</sup> test if symptoms are **severe** or if there is new-onset dysphagia with **liquids**. Barium swallow is usually done before endoscopy for the following reasons:
  - There is a risk of **perforation** when endoscoping a patient with **diverticula** or high-grade **obstruction**.
  - Information from the barium swallow may preclude the need for endoscopy.

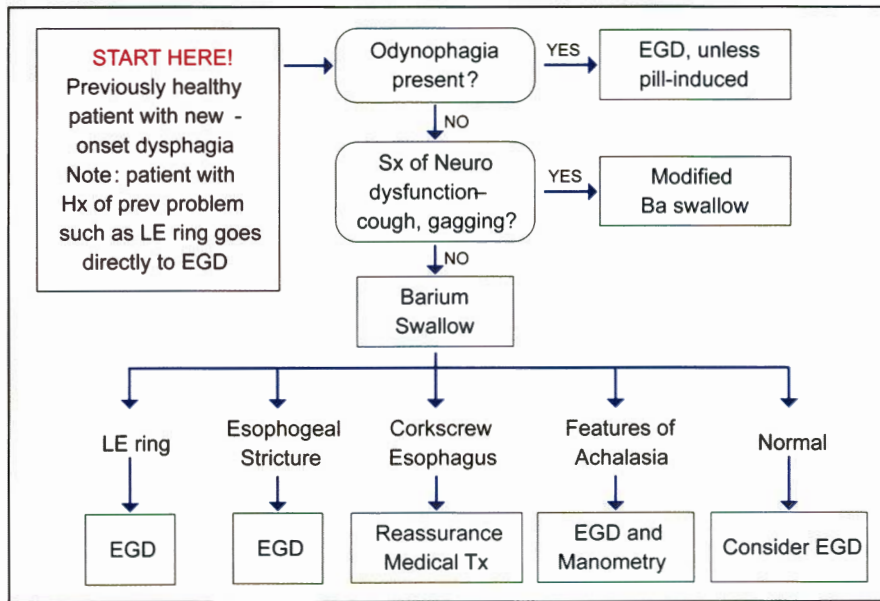


Figure 1-1: Dysphagia Workup

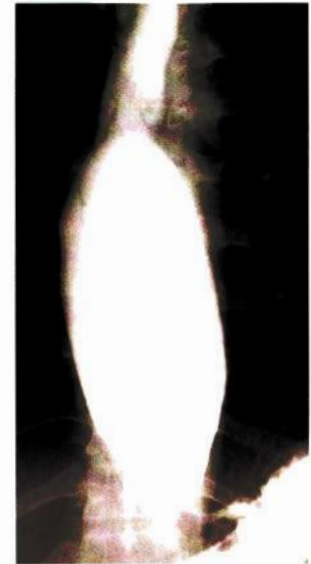


Image 1-1: Achalasia

- Information from the barium swallow provides the endoscopist a general idea of the type and severity of the underlying lesion.
- 2) **EGD** generally follows barium swallow if needed. But know that EGD can be done first if the patient has a history of reflux and presents with slight-to-moderate dysphagia for solids, because the pretest probability is high for stricture secondary to chronic reflux. Esophageal dilation can be done along with the EGD.
- 3) **Esophageal manometry** is usually done only if dysphagia persists after negative barium swallow and EGD studies.

Again, workup of dysphagia: 1 = barium swallow, 2 = endoscopy if needed, 3 = manometry studies if needed.

## ACHALASIA

Achalasia is of unknown pathogenesis, but it has characteristic and diagnostic features. Neuronal denervation and ganglion cell degeneration of myenteric plexus lead to the following findings:

- No organized peristalsis in the esophageal body.
- The lower esophageal sphincter (LES) has elevated pressure or resting tone.
- The LES does not relax with swallowing.

The characteristic features of the history include:

- Dysphagia for **solids** and **liquids**
- Long-standing symptoms, usually **years**
- **Regurgitation** of food, especially at night
- No age or gender predilection

The diagnosis of achalasia can be made by various tests, usually in this order:

- 1) Barium swallow: The esophagus will appear dilated and is often fluid-filled. The barium may take a long time to empty into the stomach, even if the patient is upright. There is a "bird-beak" narrowing distally, which represents the tight LES (Image 1-1).
- 2) EGD: Generally, the 2<sup>nd</sup> test ordered; done mainly to confirm the diagnosis and exclude a tumor at the esophagogastric junction.
- 3) Esophageal manometry: Generally done as a last test to confirm the diagnosis before treatment is offered. This test will clearly show the lack of normal peristalsis and the non-relaxing LES.

Table 1-1: Causes and Symptoms of Dysphagia

| Disease            | Main Problem        | Symptoms are ... | Symptoms precipitated by ...         |
|--------------------|---------------------|------------------|--------------------------------------|
| Schatzki Ring      | Anatomic            | Intermittent     | Solids                               |
| Stricture          | Anatomic            | Progressive      | Solids, <b>then</b> liquids          |
| Cancer             | Anatomic            | Progressive      | Solids, <b>then</b> liquids          |
| Achalasia          | Motility/Neurologic | Longstanding     | Solids <b>and</b> liquids            |
| DES                | Motility/Neurologic | Intermittent     | Solids <b>and</b> liquids (esp cold) |
| Systemic Sclerosis | Various             | Progressive      | Solids <b>and</b> liquids            |



## Quick Quiz

- What are the indications for an EGD?
- What is the 1<sup>st</sup> test usually performed in the workup of dysphagia?
- What is the common treatment for achalasia?
- A classic corkscrew pattern seen on barium swallow is indicative of what disorder?
- What type of problem causes slowly progressive dysphagia for solids and then liquids?
- What is a likely cause of anatomic obstruction of the esophagus in younger patients? In older patients?
- What anatomic problem causes slowly progressive intermittent dysphagia to solid food?

Remember the 3 tests for achalasia: barium swallow, endoscopy, and manometry.

Also remember pseudoachalasia and secondary achalasia. A tumor at the esophagogastric junction can mimic the history and diagnostic findings of achalasia. Especially consider this diagnosis if onset of symptoms is **rapid**, patient is **> 60 years**, and symptoms are **progressive** and include profound **weight loss**.

Complications of achalasia include aspiration pneumonia and weight loss.

Focus treatment for achalasia on opening the LES, usually by pneumatic dilation, in which a large, 3–4 cm diameter balloon is inflated within the LES to enlarge the sphincter. This balloon is much larger and generates higher pressure than the balloons used to treat esophageal rings and strictures. There is a 5% risk of perforation. Surgical myotomy is also very effective and can be done via laparoscope. Botulinum toxin is effective in 65% of cases but requires repeat therapy within 6–12 months. It is an alternative therapy in high-risk patients. Calcium channel blockers and nitrates have been used in the past with, at best, temporary partial relief.

## DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm (DES) is a simultaneous, nonperistaltic contraction of the esophagus, often precipitated by **cold** or **carbonated** liquids. This may be a cause of dysphagia, chest pain, or both. The chest pain is atypical in description—thus, rarely confused with cardiac ischemia. **Occult reflux** can be responsible for causing esophageal spasm in the absence of typical reflux symptoms.

Barium swallow is usually normal but may show the classic **corkscrew** pattern (Image 1-2).

Manometry confirms the diagnosis by revealing intermittent, simultaneous (nonperistaltic) contractions or high amplitude contractions. LES pressure may be low, normal, or high; i.e., nonspecific.

Endoscopy is rarely helpful. Even in those patients with spasm due to reflux, there is usually no obvious or gross reflux esophagitis. If reflux is considered a possible cause of the diffuse esophageal spasm, order a 24-hour esophageal pH recording or give twice-daily proton pump inhibitors (PPIs) for 3 months.

Treatment: Think of DES as irritable bowel of the esophagus. **Reassurance** is the most important part of therapy.

However, if reassurance is not effective or the patient requests specific therapy, recommend these in this order:

1<sup>st</sup> line: diltiazem or imipramine

2<sup>nd</sup> line: isosorbide or sildenafil

3<sup>rd</sup> line: botulinum toxin injection

Obviously, avoiding certain foods, like cold beverages, may be important. PPIs if GERD is suspected (half of pH studies are abnormal). Some patients report benefit from empiric esophageal dilation, although the rationale for this is difficult to understand, and a benefit over placebo is hard to prove.

## ANATOMIC OBSTRUCTION

### Overview

Anatomic obstruction causes a **slowly progressive** dysphagia—**initially to solids**, then to liquids when severe. Depending on the cause, this slowly progressive dysphagia may be intermittent or constant.

In **younger** patients, slowly progressive dysphagia is usually caused by a **Schatzki ring** (lower esophageal ring), whereas in **older** patients, it is usually due to **cancer** (esophageal or extrinsic compression) or **stricture**.

### Lower Esophageal Ring (Schatzki Ring)

The lower esophageal ring (LE ring or Schatzki ring) is a common cause of dysphagia, especially in **younger** patients. Patients will give a classic history of very slowly progressive, **intermittent, solid food** dysphagia, especially for meat and bread. They may have to regurgitate the



Image 1-2: Corkscrew esophagus

Courtesy of James W. Smith, MD





Image 1-3: Severe esophageal stricture on the left. Schatzki ring on the right.

impacted bolus for relief. LE ring is always associated with a **hiatal hernia**, and, although reflux may have a role in pathogenesis, at endoscopy there is usually no obvious esophagitis. On barium swallow, the ring should be 13 mm or less in diameter to cause symptoms. Treatment is dilation using either the bougie method or a through-the-scope hydrostatic balloon. Patients are placed on PPIs after dilation (Image 1-3).

### Esophageal Stricture

Esophageal stricture presents with a history of slowly progressive, **constant** (not intermittent) dysphagia for **solid foods**. Usually the stricture is due to a long history of incompletely treated **acid reflux**. The incidence of stricture has decreased sharply with the use of PPIs. It can also be due to **prolonged nasogastric tube** placement or **lye** (rare today, except in those who ingested lye decades ago; these have a chronic stricture and an increased risk of esophageal cancer). Barium swallow shows narrowing, usually at the esophagogastric junction. Treatment is dilation.

### Malignant Obstruction

Malignant obstruction can be due to esophageal adenocarcinoma, squamous cell carcinoma, or extrinsic compression from non-esophageal primary cancers. Usually the history is of **rapid progression** of symptoms: **solid food dysphagia** to **soft food difficulties** and finally to problems with **liquids** (Image 1-4).



Image 1-4: Esophageal cancer

### Plummer-Vinson Syndrome

Plummer-Vinson syndrome, a rare disorder, results in dysphagia due to an upper esophageal web. An esophageal web is a thin fold of tissue covered with squamous epithelium that protrudes into the lumen. It is usually found in **postmenopausal women** in association with **iron-deficiency anemia**—the reason for this association is unknown. There is a slightly increased risk of esophageal cancer.

### NEUROLOGIC DYSFUNCTION

Neurologic problems involving the swallowing and/or esophageal peristaltic mechanism cause dysphagia to both **solids and liquids** from time of onset.

Examples include **stroke**, **parkinsonism**, **bulbar palsy** (lower motor neuron—ALS, MS) and **pseudobulbar palsy** (upper motor neuron—ALS).

Bulbar palsy causes dysphagia due to weakness, whereas pseudobulbar palsy causes dysphagia due to disordered contractions. Any type of dysphagia can cause aspiration. This aspiration is often well tolerated and does not need treatment, unless pulmonary problems arise. These patients may complain of choking, gagging, and nasal regurgitation.

If you suspect aspiration, perform a modified or 3-phase **barium swallow** to confirm the diagnosis. Tracheostomy does not often cure chronic aspiration. A percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ) tube may be required.

Video swallowing studies are also useful in evaluating neurologic dysfunction.

### SCLERODERMA AND SYSTEMIC SCLEROSIS

Scleroderma is the term for shiny, hard, thickened skin. Scleroderma may occur alone, but when the sclerosis involves internal organs, it is called “systemic scleroderma” or “systemic sclerosis” (SSc). SSc itself can be diffuse or limited in its expression—hence the terms “diffuse SSc” and “limited SSc.”

SSc (both limited and diffuse presentations) is the most common connective tissue disease involving the esophagus. More than 80% of patients have involvement of the esophagus. When the esophagus is involved, the patient has very weak-to-absent esophageal peristalsis. The LES is “wide open” with no tone or pressure, resulting in severe acid reflux damage to the esophagus.

Dysphagia can be due to any one or a combination of the following 3 problems:

- 1) Esophagitis
- 2) Stricture
- 3) Impaired motility

## Quick Quiz

- What type of problem presents with dysphagia to both solids and liquids?
- What is the LES pressure in patients with dysphagia due to SSc?

So, workup requires a barium swallow followed by EGD to look for all 3 of these possibilities.

If esophagitis is present, begin aggressive PPI therapy. Perform a **follow-up** endoscopy at **2–3 months** to confirm healing and to assure effectiveness of the PPI dose.

Any stricture can be safely dilated using standard techniques.

Note: **Polymyositis** and **dermatomyositis** can have similar effects on the esophagus.

## EOSINOPHILIC (ALLERGIC) ESOPHAGITIS

Primary eosinophilic esophagitis (EoE) is an immune-mediated chronic eosinophil-predominant inflammatory disorder of the esophagus. Its pathogenesis involves interleukin-5 (IL-5) in a central role in concert with eotaxin.

EoE occurs most commonly in **men** age **20–40** years. There is a strong association with **allergies**—environmental, food, asthma, and atopy. **IgE** is elevated in 2/3 of patients.

The leading symptom is recurrent attacks of dysphagia with food impaction. On average, patients will have symptoms for 4–5 years before diagnosis. Symptoms are more pronounced in those with a **peripheral** eosinophilia, which is found in ~30% of patients.

The “classic” EGD finding is a **scalloped appearance** with ridges or rings in the esophagus. Diagnosis is confirmed by esophageal biopsies showing a dense eosinophilic infiltration of the esophageal epithelium (> 20 eos/HPF) in the mid-esophagus. **GERD** patients may have increased eosinophils, but only in the **distal** esophagus (**Image 1-5**).

Treatment is difficult. Most recommend referral for allergy testing and avoidance of potential allergens. Swallowed **fluticasone** (bid) or **viscous budesonide** usually results in a response within a week. Long-term therapy is usually required, and relapses are common when steroids are discontinued. PPI therapy may be helpful in those with concomitant reflux.

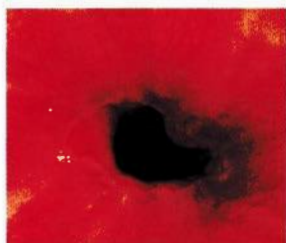


Image 1-5: Esophagitis

## MISCELLANEOUS CAUSES OF ESOPHAGITIS

Odynophagia (painful swallowing) is usually due to either pill-induced esophagitis or opportunistic infections.

### Pill-Induced Esophagitis

Pill-induced esophagitis is most likely when pills are taken with little or no water or before lying down. It is especially seen with **doxycycline** (teenager with acne), KCl, ASA, NSAIDs, iron, bisphosphonates (alendronate), and quinidine. The pain can be very severe.

Diagnosis can be made based solely on history! If the history is typical, with abrupt onset of symptoms and an obvious offending medication, no EGD is needed.

Treatment: **Stop** the offending medicine and **reassure** the patient that the condition will improve. Educate your patients to take **plenty of water** with their medications.

### Opportunistic Infections

Opportunistic infections (OIs) can occur in any immunocompromised patient, such as those with diabetes or HIV, but can also occur in an immunocompetent patient on corticosteroids. Common OIs are *Candida*, herpes simplex virus, and cytomegalovirus. If you see thrush in the mouth, you can assume that the esophagitis is also due to *Candida*; treat the patient empirically with **fluconazole**. If there is no improvement, or you're unsure of the diagnosis, EGD with biopsy is the procedure of choice. Rarely is dilation needed or helpful.

## PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are more commonly used today than H<sub>2</sub> receptor blockers because they are generally more effective.

Efficacy of the PPIs depends on plasma levels. They are all metabolized via the cytochrome P450 pathway with CYP2C19 being the main enzyme. There is a genetic **mutation** for this enzyme that results in a person being a “**slow metabolizer**.” **Heterozygotes** are **moderate metabolizers**, and the people without the mutation (i.e., **wild type**) are **rapid** metabolizers. The proportion of slow metabolizers varies by ethnicity. For instance, among Caucasians, it is 5%, 30%, 65%; slow to fast. **Slow** metabolizers of PPIs have **much better results** than fast metabolizers.

PPIs cause hypergastrinemia, achlorhydria, and possibly gastric atrophy. Short-term and long-term effects of PPIs are becoming known.

Short-term: **Community-acquired pneumonia** (CAP) appears more likely to occur within 30 days of starting PPIs—and especially within 48 hours.



Long-term:

- **Fracture** risk appears increased
- **Hypomagnesemia** (muscle spasms, arrhythmias, seizures)

Although long-term PPI use leads to parietal cell hyperplasia, no dysplasia or neoplasia has been seen.

**Rebound acid hypersecretion** occurs when PPIs are stopped abruptly after several months—especially in *H. pylori*-negative patients.

Long-term use of PPIs is now discouraged unless necessary (e.g., Barrett esophagus).

Drug interactions with PPIs:

PPIs interact with few drugs and are generally well tolerated. They **decrease** absorption and blood levels of **thyroxine** and **itraconazole/ketoconazole** and **increase** absorption of **digoxin**.

A controversy regarding use of clopidogrel with omeprazole has been resolved by the COGENT trial and a subsequent consensus statement (ACC/AHA/ACG in December 2010) which states:

- There is no significant cardiovascular harm found.
- There is potential GI protective effect.
- Further study is needed for the slow metabolizers of clopidogrel.

## GE REFLUX DISEASE (GERD)

### Overview

GE reflux is usually a result of inappropriate, transient relaxation of the lower esophageal sphincter (LES). The transient relaxation is, in part, a reflex caused by recently ingested fat in the duodenum or by overdistension of the stomach. Hiatal hernia is another factor—but it is not necessary for reflux.

LES pressure is **increased** by motilin, acetylcholine, and possibly gastrin. Therefore, drugs that increase these mediators tend to decrease reflux. LES pressure is **decreased** by progesterone (pregnancy increases GE reflux), chocolate, smoking, and some medications, especially those with anticholinergic properties.

Suspect GE reflux disease (GERD) in patients with a persistent, nonproductive cough, especially with hoarseness, continual clearing of the throat, and a feeling of fullness in the throat. This cough is usually worse at night when the patient is supine.

Most non-cardiac chest pains (70%) are caused by GERD! Most other GI-related chest pains are due to motility disorders. Note: These pains are not necessarily associated with pyrosis (heartburn) or dysphagia.

Extraesophageal manifestations of GERD:

- Nocturnal cough
- Frequent sore throat

- Hoarseness, laryngitis, clearing of the throat
- Loss of dental enamel
- Exacerbation of asthma
- VCD (vocal cord dysfunction)

GERD is associated with two respiratory disorders: asthma and VCD.

Some asthma patients, even without symptoms of GERD, have improvement of their asthma symptoms with GERD treatment. When working up GERD, always ask about asthma symptoms—especially those occurring at night. Note: A recent study showed that treatment of asymptomatic GERD in patients with severe asthma did not improve asthma control. More in the Pulmonary section, Book 2.

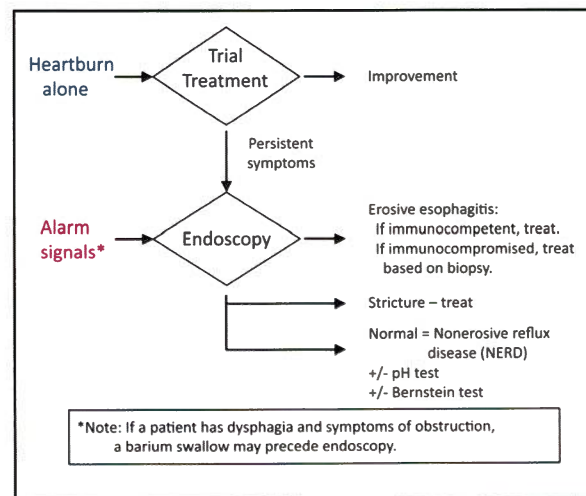
Do not assume asthma is the cause in patients who complain of nocturnal symptoms. VCD is spasm of the vocal cords with associated **inspiratory** stridor. Patients will tell you they are wheezing at night and may not really know if it is inspiratory or expiratory. VCD is not always due to GERD; it is more typically seen in young adults in competitive sports and is thought to be more of a stress reaction. About 10% of exercise-induced “asthma” is now thought to be misdiagnosed VCD.

Increased body mass index (**BMI**) is associated with increased incidence of both GERD and asthma.

Complications: esophageal ulcers, stricture, bleeding, and Barrett esophagus (discussed on [page 1-8](#)).

### Diagnosis of GERD

If the patient has only the classic symptoms of heartburn **without alarm signals**, the diagnostic workup starts with a therapeutic trial of PPIs—EGD is indicated only if this trial fails ([Figure 1-2](#)).



**Figure 1-2: Workup of Suspected GERD**



## Quick Quiz

- Which drugs interact with PPIs?
- What is the clinical presentation of GERD?
- What are the “alarm” signals in a patient with GERD symptoms? These indicate the need for what?
- For how long is severe GERD treated? And with what?
- In patients with GERD, what study must be done before antireflux surgery?

**Alarm signals** in GERD indicating the need for **EGD**:

- Nausea/emesis
- Blood in the stool
- Family history of PUD
- Weight loss
- Anorexia
- Anemia
- Abnormal physical exam
- Long duration of frequent symptoms, especially in Caucasian males > 45 years old
- Failure to respond to full doses of a PPI
- Dysphagia/odynophagia

EGD also is done if you suspect Barrett esophagus.

If the patient has obstructive symptoms, you can do a barium swallow before endoscopy.

Note: 62% of patients with GERD symptoms have a normal esophagus. This is termed nonerosive reflux disease, or NERD!

Conduct the 24-hour esophageal **pH monitor** for atypical cases, such as:

- Refractory symptoms and a normal EGD
- Hoarseness, coughing, or atypical chest pain, but no classic symptoms of GERD
- Failure to respond to PPIs

The pH monitor is similar to a Holter monitor in that the patient keeps a diary of symptoms. You then analyze the diary logs and pH monitor results for correlation.

## Treatment of GERD

Treatment of **mild-to-moderate** GERD:

Initial:

- **Raise head of bed.\***
- Encourage **weight loss of > 10 lb** if overweight or there was recent weight gain.\*
- Small meals, no fatty meals in the evening, eat dinner at least 3 hours before bedtime, no sweets at bedtime.

- Stop smoking.
- Antacids prn.
- Avoid alcoholic and acidic beverages before bedtime (e.g., colas, orange juice, wine).

\*In clinical trials, only these 2 have been shown to be effective; the rest are more “common sense” but not proven by studies to do anything more than placebo.

If the above is unsuccessful, try **antisecretory** drugs:

Overall healing of patients with endoscopic evidence of **esophagitis** (not necessarily GERD!):

- Placebo: 25%
- H<sub>2</sub> blockers and prokinetic drugs: 50%
- PPIs: **80–95%**

H<sub>2</sub> blockers may heal mild cases of GERD, but treatment of **severe GERD** (i.e., grade 2 or worse esophagitis) **requires PPIs**, such as omeprazole or lansoprazole, continued **indefinitely\***, unless the patient has corrective surgery.

PPIs in particular are indicated for **long-term** therapy\* in patients with EGD evidence of **esophagitis**.

\*Note the concerns with the long-term use of PPIs in the previous topic, Proton Pump Inhibitors.

In patients with GERD symptoms who do not respond to PPIs, check for other medications that may delay gastric emptying and thus promote reflux—especially calcium channel blockers, antihistamines, tricyclics, and anticholinergics.

Consider antireflux surgery (fundoplication, now mostly laparoscopic) in patients with severe GERD because it has a reasonable success rate. Indications: patients **refractory** to medical treatment, **young** patients with **severe** disease, and as an **alternative** to long-term PPIs. Outcome of antireflux surgery is best in patients responding to PPIs. However, even after reflux surgery, 60% will still require PPI therapy. With Nissen fundoplication, the lower esophagus is wrapped in a sleeve of the stomach. Side effects of this surgery are bloating, dysphagia, and an inability to belch. You must do a motility study prior to antireflux surgery—because the results may influence the performance of the fundoplication. Patients with very poor peristalsis are at risk for postoperative dysphagia. Endoscopic antireflux procedures are not ready for routine use.

Treat peptic strictures secondary to GERD with dilation and then PPIs. Note: Metoclopramide (due to too many side effects) and sucralfate (not very effective) have **little use** in treatment of GE reflux.

Maintenance therapy consists of PPIs for moderate-to-severe cases. Long-term use of H<sub>2</sub> receptor blockers is usually ineffective.

Be aware that patients with GERD-related cough/hoarseness require longer treatment and higher doses (e.g., bid) for symptomatic improvement of the cough or hoarseness than those with run-of-the-mill heartburn.

## BARRETT ESOPHAGUS

Barrett esophagus is a change in cell type—from esophageal **squamous** to specialized intestinal **metaplasia**—caused by chronic GE reflux. Even though GERD is the cause, many patients with Barrett esophagus lack reflux symptoms.

10–20% of men endoscoped for chronic reflux have Barrett esophagus! And about 2% of women.

The need for **screening** for Barrett's is a **controversial** topic because of the lack of randomized clinical trials that have shown any impact on mortality with screening. Even so, the current guidelines do support surveillance screening based on retrospective studies. According to these guidelines, the highest yield for Barrett's screening is in older Caucasian males (> 50 years) with long-standing heartburn (> 10 years).

Barrett esophagus is associated only with **adenocarcinoma** (not squamous). Incidence of adenocarcinoma in patients with Barrett esophagus is **30x** the normal rate. Probability of adenocarcinoma is related to the length of Barrett esophagus, presence of a hiatal hernia, degree of dysplasia, and concurrent smoking. Risk of adenocarcinoma is 0.4% per year in patients with Barrett esophagus (**Image 1-6**). Neither anti-reflux medication nor surgery reverses the epithelial changes of Barrett esophagus—or eliminates the cancer risk.

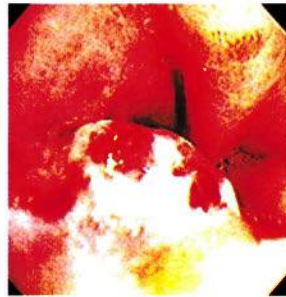


Image 1-6: Barrett esophagus

If Barrett esophagus is found, do follow-up endoscopic surveillance as follows (2011 ACG guidelines):

- No dysplasia: 3–5 years
- Low-grade dysplasia: 6–12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months

Endoscopic surveillance includes 4-quadrant biopsies every 2 cm if no dysplasia, every 1 cm for known dysplasia.

For any **high-grade** dysplasia, **eradication therapy** is now recommended over surveillance.

Endoscopic eradication therapy is the treatment of choice. It is done with radiofrequency ablation (RFA) or endoscopic mucosal resection (EMR). Photodynamic therapy (PDT) is occasionally used.

Esophagectomy is an alternative for high-grade dysplasia but has **higher morbidity** and should be done by centers that **specialize** in this type of surgery.

## ESOPHAGEAL CANCER

Two types of esophageal cancer: **adeno** and **squamous** (~ 50% each).

**Adenocarcinoma** of the esophagus has been on the rise (from Barrett esophagus) and now occurs more commonly than squamous cell; it occurs in the **distal 1/3** of the esophagus. See more in previous discussion.

**Squamous cell** esophageal cancer usually occurs in the **proximal 2/3** of the esophagus, and it is caused by **smoking** and **alcohol** (especially hard liquor). It is associated with other cancers of head or neck and is rarely associated with achalasia, lye stricture, or Plummer-Vinson syndrome (see **page 1-4**).

Smoking and alcohol have a **synergistic** (not additive) carcinogenic effect on the esophagus. Incidence of squamous cancer has a marked geographic variation, and its occurrence appears to be strongly associated with **diet** and **environment**.

Diagnosis of esophageal cancer is accomplished with a number of tests. **Dysphagia** is the usual presenting symptom, so a barium swallow during the workup may suggest cancer. EGD is always done to allow confirmation via **biopsy**. Use CT scan and endoscopic ultrasound to stage the tumor.

If small and localized, do surgical resection. If large or metastasized, treat with combination chemotherapy (cisplatin + 5FU) plus radiation prior to surgery. This combination results in a 2-year survival of 38% vs. 10% with radiation alone.

## ZENKER DIVERTICULUM

Zenker diverticulum is an outpouching of the **upper** esophagus. Patients have **foul-smelling breath** and may **regurgitate** food eaten several days earlier. This is the most common cause of **transfer dysphagia** (trouble initiating swallowing) for solid foods, but it can also cause transport dysphagia. These patients are often elderly. Treatment is surgery.

[Know the indications for EGD, ERCP, pH monitor, and motility studies!]

## STOMACH

### NORMAL PHYSIOLOGY

First, a quick review of normal stomach physiology as it relates to gastritis and peptic ulcer disease (PUD). See **Figure 1-3**. The light green highlight shows the main pathway used in production of gastric acid.

G cells are in the pyloric antrum. Increase in pH and amino acids (from food breakdown) cause the G cells to release gastrin which, like acetylcholine (ACh) and histamine, interacts with specific receptors on the parietal cells in the fundus—stimulating them to secrete (via the proton pump) HCL (gastric acid) into the lumen. Gastrin



## Quick Quiz

- What is the pathologic definition of Barrett esophagus?
- What cancer is associated with Barrett's?
- What follow-up is indicated in patients with Barrett's?
- What is the treatment of choice for Barrett's with high-grade dysplasia?
- Discuss the differences between adeno and squamous cell cancer of the esophagus.
- Name the risk factors for esophageal cancer.
- What is the clinical presentation of dyspepsia?

additionally (and more importantly) stimulates enterochromaffin-like (ECL) cells to produce histamine.

The proton pump is the final common pathway for the action of these 3 receptors and why PPIs are the strongest anti-gastric acid drugs.

**Gastrin** is released into the circulation and is therefore an endocrine stimulus for gastric acid release. Gastrin is the dominant mediator of postprandial gastric acid production.

**Histamine**, released by the ECL cells in the corpus—especially due to gastrin stimulation—has a local paracrine effect via the  $H_2$  receptors of the parietal cells.

**ACh** (acetylcholine), from the vagus nerve, has a direct neurocrine effect on the parietal cells.

Therefore, parietal cells are affected by **endocrine**, **neurocrine**, and **paracrine** stimuli.

**Somatostatin** and **secretin** both decrease the production of gastrin (and therefore gastric acid), and the production of both of these is stimulated by low pH—hence, they are the negative feedback portions of the regulatory mechanism for maintaining stomach pH. A stomach  $pH < 3$  causes production of somatostatin by corpus D cells. Secretin is produced in the duodenum in response to the acidified output of the stomach; it both **decreases** the **gastrin** production and **stimulates output of bicarbonate** from the pancreas. Again, 2 inhibitors of gastrin (and therefore gastric acid) production are somatostatin (low stomach pH) and secretin (low duodenum pH).

Note: In patients with achlorhydria (as in autoimmune gastritis, see next page) or pernicious anemia, the serum gastrin level skyrockets because of the loss of this inhibitory effect. If PPIs result in achlorhydria, they can secondarily result in a markedly elevated gastrin level ( $> 500$  pg/mL).

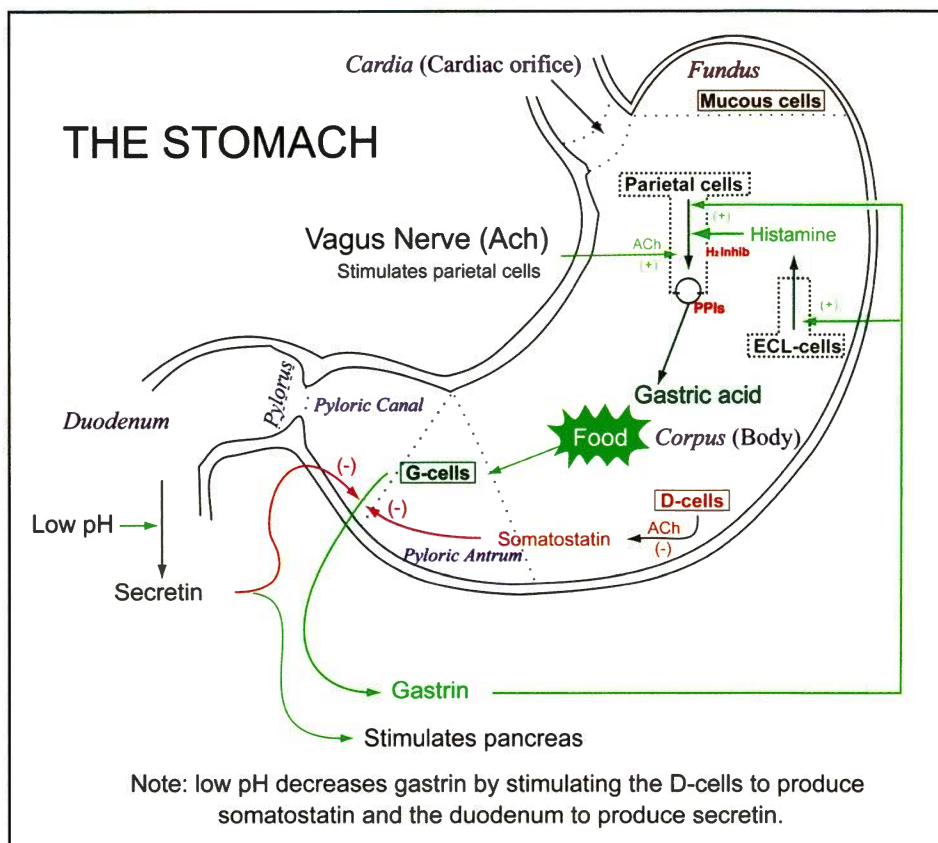


Figure 1-3: Stomach Physiology

Both gastric acid and pepsin (made from pepsinogen in the presence of acid) not only digest food but also attack the mucosal defenses.

Things to know about the mechanical actions of mixing and grinding:

- This is best studied with a gastric emptying scan.
- Only particles  $< 1$  mm can pass the pylorus.
- Peristalsis is activated by a pacemaker.

## DYSPEPSIA

Dyspepsia is a nonspecific term that refers to recurrent upper abdominal pain or discomfort. It includes **epigastric fullness**, **belching**, **bloating**, **gnawing pain**, and **heartburn**. It generally does not apply to severe pain. Most dyspepsias are **functional** or caused by **medications**.



(e.g., Fe, ASA, NSAIDs), but if onset is recent, there are no medicines involved, and the patient is > 40 years, consider an organic cause; i.e., consider an EGD. For patients < 55 years, test for *H. pylori* and treat if positive (more below).

Organic causes of dyspepsia include PUD, gastritis, GERD, biliary colic, gastroparesis, pancreatitis, and cancer. EGD is usually normal. Dyspepsia is generally classified by symptoms: **GERD-like**, **ulcer-like** (improves on anti-ulcer therapy), and **dysmotility-type** (improves on promotility drugs, such as metoclopramide). There can also be overlaps in the types.

“**Non-ulcer** dyspepsia” is defined by recurrent upper abdominal pain with a normal EGD.

So, how do we handle dyspepsia?

- Conduct a workup
- Test and treat if *H. pylori* +
- Discontinue NSAIDs
- Conduct a PPI treatment trial
- Order EGD if alarm symptoms or failure of therapy

## GASTRITIS

### Classification Schemes

Gastritis is generally classified by **histology** or **etiology**.

### Classification by Histology

A neutrophil infiltrate is seen in acute gastritis, while a lymphocyte and plasma cell infiltrate occurs with chronic gastritis. Histologic classification reflects the findings throughout the possible life of the disease:

- Superficial gastritis (early, neutrophils)
- Atrophic gastritis (mid, lymphocytes)
- Gastric atrophy (late, gastropathy)—also called metaplastic atrophic gastritis

Some lump mid and late disease into a single term, “chronic gastritis,” which is not quite correct—the inflammation has “burned out” in the late phase, so it is not really a gastritis. Biopsy of gastropathy shows atrophy of gastric glands with fibrosis but no inflammatory infiltrate.

### Classification by Etiology

**Type A:** Autoimmune, **A**trophic, pernicious **A**nemia, **A**chlorhydria. It affects the **proximal** stomach—fundus and body only. (Note: “Antrum” is not one of the “A” words!) Autoantibodies against both intrinsic factor and the parietal cells cause a progression to pernicious anemia and to achlorhydria, with secondary hypergastrinemia (levels often > 1,000 pg/mL). Metaplasia is a universal feature of atrophic gastritis; it appears before, and is associated with, both pernicious anemia and gastric cancer. Even so, the incidence of gastric cancer

is so low with atrophic gastritis that, if there is no cancer or dysplasia on initial endoscopic exam, periodic endoscopic exams are not warranted!

**Type B** is the **most common** form of chronic gastritis (80%). It is a treatable infectious disease caused by *Helicobacter pylori*. Symptoms and findings can mimic Type A gastritis.

But ... successful treatment of the infection results in resolution of gastritis symptoms in less than half the patients!

Gastric acid secretion decreases with increased degree of *H. pylori* gastritis. Oral meds such as itraconazole, ketoconazole, and thyroxine **require gastric acid** for optimal absorption. Note: 50% of AIDS patients have decreased stomach acid and are especially prone to itraconazole failure. Fluconazole does not require gastric acid for proper absorption.

Especially remember **thyroxine** because this widely used drug has been shown to require gastric acidity for optimal absorption.

### Erosive Gastropathy

Erosive gastropathy, frequently with subepithelial hemorrhage, may be caused by **NSAIDs**, **alcohol**, or **severe physiologic stress** (Image 1-7).

Note that gastritis, by definition, means there is an inflammatory response; however, there is not one in this setting. So, calling this a gastritis, as is commonly done, is technically wrong.

Onset of erosive gastropathy in the ICU suggests stress-related mucosal damage (**SRMD**), which is due to severe physiologic stress, such as that induced by major surgery or burns. Having severe CNS injuries, being on a ventilator, or having a coagulopathy are also major risk factors. Just about **anything** works to prevent SRMD:  $H_2$  receptor antagonists, antacids, PPIs, sucralfate, and even early feedings decrease the incidence of erosive gastropathy.

Continuous infusion of an  $H_2$  receptor antagonist is the **most effective** treatment for SRMD. Although it was thought that decreased acidity in the stomach allowed colonization and increased the risk of aspiration pneumonia, it has been shown that there is no increase in aspiration pneumonia with the use of  $H_2$  blockers.

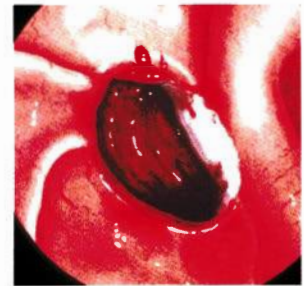


Image 1-7: Acute erosive gastritis

## Quick Quiz

- What are the possible approaches for dyspepsia?
- When should you test for *H. pylori*?
- Is the CLOtest accurate if a patient is taking a PPI? What other *H. pylori* tests are affected by PPIs?
- Which type of *H. pylori* test is not good for checking effectiveness of treatment?
- What is a common medical regimen for *H. pylori* infection?

## MORE ON *H. PYLORI*

### Overview

*H. pylori* infection is linked to **gastritis** and also **PUD**, **gastric adenocarcinoma**, and **gastric B-cell (MALT) lymphoma**.

Chronic gastritis occurs in all people infected with *H. pylori*, although only a minority have symptoms. Treat only **symptomatic** patients.

Virtually all people in third world countries are infected with *H. pylori*. In the U.S., the incidence is ~ 50% in older patients and 30% overall. It is usually acquired in childhood. Incidence is decreasing in the U.S.

### Testing for *H. pylori*

[Know!] Test for *H. pylori* when:

- there is any prior history of PUD, complicated or uncomplicated, and especially duodenal ulcer,
- current findings on EGD show ulcer disease, erosive gastritis, or duodenitis,
- MALT lymphoma is present, and/or
- there is a family history of gastric cancer.

The strategy is “test and treat” in dyspeptic patients < 55 years of age even with no alarm symptoms/features.

### Invasive tests:

- The **gold standard** for *H. pylori* testing is histologic examination of biopsied antral mucosa—done during EGD.
- Urease tests are based on the finding that *H. pylori* breaks down urea into ammonia and CO<sub>2</sub>. Urease tests are good for checking for **active disease** and for **response to therapy**. These tests are sensitive (95%) and specific (95%). For the **CLOtest**® and other rapid urease tests (RUT), the biopsy sample is placed on an agar medium containing urea and a pH reagent. Any ammonia then produced causes an increase in pH, which changes the color of the medium. Urease tests are less sensitive if the patient is on a drug that may blunt the effect of *H. pylori* infection, such as **PPIs**

and **antibiotics**. In such patients, it is appropriate to obtain biopsies for histology with or without RUT or to plan testing with a urea breath test or fecal antigen test later (after withholding the offending agents for 2–4 weeks).

**Noninvasive** tests include a urea breath test, a fecal antigen test, and a serologic test:

- A urea breath test (UBT), which uses labeled urea, is the 1<sup>st</sup> choice for checking effectiveness of treatment.
- A fecal antigen test (FAT) is a good method for primary diagnosis, and if the patient is on PPIs, it is the best test for checking effectiveness of treatment (S&S = 94% & 98%).
- Serologic tests are no longer recommended due to their low PPV (positive predictive value; < 50%). Also, serum tests are poor for checking effectiveness of treatment.

Again:

PPIs interfere with any urease test (CLOtest and urease breath test). Stop PPIs 2 weeks before the breath test.

Serologic tests are discouraged due to poor positive predictive value.

PPIs and *H. pylori* gastritis cause decreased gastric acid production which, in turn, interferes with absorption of some medications (thyroxine, azole antifungals).

### *H. pylori* Treatment

*H. pylori* treatment is the same whether the patient has gastritis or PUD:

- Treat for 10–14 days.
- Usually, triple-drug therapy is used—2 antibiotics and a PPI. A good one with an eradication rate of ~ 80% is O-CLAM (omeprazole 20 mg + **clarithromycin** 500 mg + **amoxicillin** 1 gm—all bid x 10–14 d). Recurrence rate is very low.

Know: The more drugs the better! Single- and dual-drug therapies are ineffective.

Note: *H. pylori* develops resistance to metronidazole and clarithromycin when used alone—so any recent use of these antibiotics precludes their use. Also, regimens that include **metronidazole** are **less effective** in the U.S. than in Europe—probably because there is increased resistance to metronidazole in the U.S. If the 1<sup>st</sup> course of therapy (PPI and 2 antibiotics) fails to eradicate *H. pylori*, then some recommend PPI + amoxicillin + levofloxacin.

Universal post-treatment testing is not recommended. The accepted indications include the following:

- History of *H. pylori*-associated ulcer
- Persistent dyspepsia despite the test-and-treat strategy
- *H. pylori*-associated MALT lymphoma
- Resection of early gastric carcinoma

When confirmation is necessary, testing should be



performed no sooner than 4 weeks after the completion of therapy. In general, noninvasive tests (not serology) should be done for posttreatment testing unless there is a need for repeat EGD.

## PEPTIC ULCER DISEASE (PUD)

### ETIOLOGY

Peptic ulcer disease (PUD) has 4 well-confirmed causes:

- 1) *Helicobacter pylori* infection is still the most common cause of PUD—especially duodenal ulcer disease (50%, but incidence is **decreasing** in the U.S.). Life-time ulcer risk for a person with *H. pylori* infection is 10–15% (higher for men). If *H. pylori* can be eradicated, ulcers virtually never recur, and the *H. pylori* recurrence rate is very small. The trouble is getting rid of it! If the ulcer does recur, suspect NSAIDs. See earlier discussion of *H. pylori* testing.
- 2) NSAIDs cause the majority of peptic ulcers not caused by *H. pylori*. The prevalence of ulcers in patients on NSAIDs is 10–30% (!) although many are < 5 mm and asymptomatic. NSAIDs cause both gastric and duodenal ulcers—usually gastric. If NSAIDs are required, and the patient is having or has had trouble, use any of the following:
  - **Nonacetylated** NSAIDs (e.g., salsalate).
  - NSAIDs that are **non-acidic prodrugs** (e.g., nabumetone; Relafen®).
  - NSAIDs with a **PPI** or prostaglandin E analog (e.g., **misoprostol**). PPIs are superior to H<sub>2</sub> blockers and sucralfate in the prevention of NSAID-induced ulcers.
  - **COX-2** NSAIDs (see next page).

Enteric-coated NSAIDs have been recommended in the past; but the 2008 ACC/ACG guidelines on NSAIDs in patients with coronary artery disease highlights data that demonstrates no increased benefit of enteric-coated formulations in reduction of GI adverse events.

Risk factors for conventional NSAID-induced PUD include: first 3 months of use, high doses, elderly patient, history of ulcer disease or prior UGI bleed, cardiac disease, concurrent steroids, serious illness, and concurrent ASA (such as for cardioprotection).

- 3) High acid-secreting states, such as Zollinger-Ellison (1–3% of duodenal ulcers).
- 4) Crohn disease of the duodenum/stomach.

What about smoking? In gastric and duodenal ulcer disease, smoking exacerbates the ulcer. For non-*H. pylori* ulcers, smoking also decreases the healing rate and increases recurrence and perforation rate. Commonly, these recurrences are asymptomatic.

Previously, the incidence of PUD was higher in men, but now the male-to-female ratio is approaching 1. Type of

diet, personality, and occupation are not significant etiologic factors in PUD! Weight loss is uncommon in PUD.

Notes: **Alcohol** is not ulcerogenic! **Corticosteroids** alone are not ulcerogenic, but they **double** the risk of serious NSAID-associated gastrointestinal complication—risk of bleeding may be **10-fold**!

### DIAGNOSIS OF PUD

The following are currently approved strategies for diagnosing PUD:

- For the **younger, healthy** patient with classic symptoms, no diagnostic protocol is required—empiric treatment with an H<sub>2</sub> blocker or PPI is acceptable.
- For this same **younger, healthy** group, *H. pylori* “test-and-treat” also is acceptable.
- **EGD** is done for **all other patients**, particularly if melena, heme+ stools, or in an older patient.

EGD is always indicated in PUD in the following situations:

- If associated with dysphagia and odynophagia
- Follow-up for a healing **gastric** ulcer
- UGI bleeding
- Foreign body
- Abnormal UGI (barium swallow) or CT scan
- Family history of duodenal ulcer disease

The upper gastrointestinal series (UGI) is less sensitive than the EGD and rarely done today to diagnose PUD. If an ulcer is found, serum gastrin levels may be indicated (specifics discussed under the type of ulcer). Diagnose the presence of *H. pylori*, as described in the Gastritis section, [page 1-10](#).

**Perforated** gastric and duodenal ulcers often cause free air in the peritoneal space, which can be seen on an upright abdominal x-ray. If a perforated ulcer is suspected, do the upright x-ray first! EGD and UGI are **contraindicated**. Also know that absence of an ulcer crater means there is no risk of hemorrhage, perforation, or scarring.

Know: The pain of an ulcer tends to be gnawing, whereas that of a perforated ulcer is usually severe.

### TREATMENT OF NONBLEEDING PUD

Treatment of PUD targets combinations of 3 main strategies:

- 1) *H. pylori* treatment
- 2) Decrease acid secretion (H<sub>2</sub> receptor antagonists, PPIs)
- 3) Stop exacerbating processes (smoking, taking NSAIDs)

Less frequently used are mucosal protection (sucralfate) and acid neutralization with antacids.



## Quick Quiz

- What is the most common cause of peptic ulcer disease?
- What is the relationship between NSAIDs and PUD?
- How does smoking affect PUD?
- What is the relationship of steroids to PUD? Alcohol?
- How are peptic ulcers diagnosed? If perforated?
- Name at least 3 indications for surgery in a patient with PUD.
- What is the main cause of bleeding ulcers in the U.S.?

Treat *H. pylori* infection associated with PUD. This is discussed on [page 1-11](#).

If the patient tests negative for *H. pylori* infection, and if exacerbating factors such as NSAIDs have been addressed, then use antisecretory drugs and antacids.

Sucralfate is effective treatment of non-*H. pylori* PUD, but patients do not care for the qid dosage; so **PPIs are preferred**. At the ulcer site, sucralfate binds bile salts and forms a barrier that prevents acid penetration. Sucralfate is a **short-term** drug of choice in renal patients because it also binds  $\text{PO}_4$ . However, sucralfate should not be used long term in patients with advanced chronic kidney disease, because it can cause aluminum accumulation and metabolic bone disease.

Stop smoking—smoking increases risk of recurrence and perforation in ulcers not associated with *H. pylori* or in untreated *H. pylori* ulcers.

Indications for surgery in PUD:

- **UGI bleed**—most common—active bleed unable to stop via endoscopic therapy. Surgery is required in 5% of UGI bleeds.
- Gastric outlet **obstruction**—initial treatment is balloon dilation. Surgery required in ~ 25%.
- **Perforation**—laparoscopic repair may be possible.
- **Recurrent/refractory** ulcers (rare).
- **Zollinger-Ellison syndrome (ZES)**—surgery is for underlying gastrinoma.

## DUODENAL vs. GASTRIC ULCER

Duodenal ulcers: Again, the common causes are NSAIDs and *H. pylori*, and only 1–3% are due to increased acid secretion (ZES). See [Image 1-8](#) and [Image 1-9](#).



Image 1-8: Duodenal ulcer

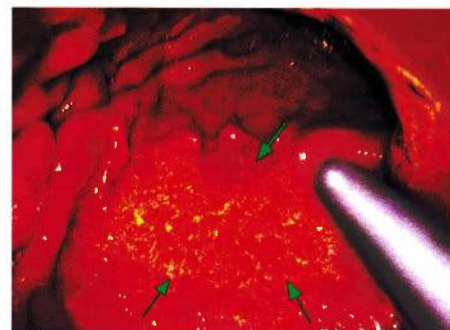


Image 1-9: Gastric ulcer

Gastric ulcers not associated with *H. pylori* are treated for 3 months because these **heal more slowly** than duodenal ulcers. **PPIs** and **misoprostol** (a synthetic prostaglandin) are superior to  $\text{H}_2$  blockers and sucralfate in the prevention of NSAID-induced ulcers.

Although gastric ulcers were previously thought to increase gastric cancer risk, studies have not shown this to be true! On the other hand, examine all **nonhealing** gastric ulcers via endoscopy with a cytologic exam of at least **6** biopsy samples to rule out **gastric cancer**.

## BLEEDING PEPTIC ULCERS

### NSAIDs

NSAIDs are the leading cause of **bleeding** ulcers in the U.S. Ulcer symptoms may not occur before bleeding. The bleeding risk is **dose-related**. As mentioned previously, corticosteroids alone are not ulcerogenic, but they may increase the NSAID-associated bleeding 10-fold!

**Risk of bleeding** with conventional NSAIDs:

- General population: 1%
- In those using aspirin concurrently as preventive medicine: 1.5%
- History of PUD/UGI bleed: 3%

NSAID-related ulcer risk is higher in any patient > 60 years of age and in any female.

If you add cardiac disease to any of the above factors, the risk triples. Note that there is no perfectly safe dose of aspirin.

**Risk of bleeding** with **COX-2** NSAIDs:

- COX-2 used alone has close to normal risk of GI bleeding (0.5%).
- COX-2 with low-dose (81 mg) aspirin has the same risk as regular doses of NSAIDs (1%)! Baby aspirin used alone has near-normal risk of GI bleeding.

COX-2 NSAIDs block the action of cyclooxygenase (COX), an enzyme that converts arachidonic acid to prostaglandin. COX-1 is the constitutive enzyme, while COX-2 is inducible. COX-1 produces protective prostaglandins in the stomach, whereas the inducible

COX-2 is involved in inflammatory response. COX-2 inhibitors (celecoxib, Celebrex®; meloxicam, Mobic®) appear to have **decreased GI side effects** (compared to conventional nonselective NSAIDs), while retaining the antiinflammatory and pain relief effects.

All NSAIDs (including COX-2 inhibitors) appear to have some **cardiovascular risk** (thrombosis and MIs) that may vary from one to the other and generally are related to dose.

All NSAIDs now have an FDA-mandated **boxed warning** highlighting the potential for increased risk of death from **cardiovascular events** and **GI bleeding**.

### Workup of Bleeding Peptic Ulcers

Signs indicating a **severe** bleed and high risk of rebleed:

- Hemodynamic instability
- Recurrent red-colored hematemesis or hematochezia
- Lack of clearing of gastric lavage effluent

EGD is the diagnostic and treatment procedure of choice for UGI bleed. It should be done emergently if the patient has any of the above findings.

EGD is done for 2 reasons:

- 1) To treat the current bleed
- 2) To assess the risk for rebleed

EGD findings that indicate increased chance of rebleed:

- 1) Larger size of the ulcer.
- 2) Visible vessels on a non-bleeding ulcer (increase the risk for rebleed to 50%). See [Image 1-10](#).
- 3) Visible clot = 30%.

An ulcer with a clean base (i.e., no bleeding, no clot, and no visible vessels) has a very low chance of rebleed. These patients are usually sent home the same or next day—unless they have 1 of the 3 signs of severe bleed mentioned above.

### Treatment of Bleeding Peptic Ulcers

What does not work: Gastric lavage does not stop bleeding or prevent rebleeding. IV vasoconstrictors also are ineffective.

The purpose of gastric lavage is to look for blood in the effluent. Blood in the effluent indicates the stomach is the source of bleeding but remember the absence of blood does not rule out peptic ulcer as the source because it may have stopped bleeding.

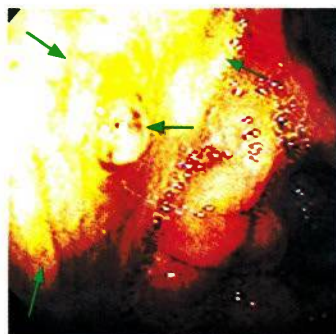


Image 1-10: Ulcer with visible vessel

Increasing the gastric pH to  $> 6.0$  reduces the risk of rebleeding—PPIs given either IV or orally bid achieve this. Most patients with a bleeding ulcer get prompt IV PPI treatment before endoscopic banding or sclerotherapy; this is continued until they are able to switch to oral bid therapy.

Initial treatment of actively bleeding ulcers (or adherent clot/visible vessel) shows best results with combination therapy consisting of injection (epinephrine, saline, alcohol) followed by either thermal/laser coagulation or a hemoclip.

### NON-ULCER CAUSES OF UGI BLEEDS

**Osler-Weber-Rendu** (hereditary hemorrhagic telangiectasia) causes telangiectasias on the skin, buccal and nasal mucosa, and throughout the GI tract, lungs, and brain. Occasionally arteriovenous malformations (AVMs) occur, and these can rupture and bleed. In the GI tract, these AVMs are usually in the stomach or duodenum.

**Peutz-Jeghers syndrome** (PJS) causes dark melanin spots on the lips, buccal mucosa, and the hands and feet. Most patients have hamartomatous polyps that can occur anywhere from the stomach to the rectum. These polyps may cause acute or chronic GI bleeds.

### ZOLLINGER-ELLISON

Zollinger-Ellison syndrome (ZES) occurs when a **gastrinoma**, which produces gastrin continuously, causes refractory (usually duodenal bulb and stomach) ulcers and **diarrhea +/- steatorrhea**. The most common presentation of ZES is diarrhea. The diarrhea/steatorrhea is from a large volume of gastric juice, causing acidification of duodenal contents.

Gastrinomas most frequently occur in the duodenum (~ 50%) or pancreas (~ 25%), and less frequently in the stomach, lymph nodes, and spleen. 90% are found in what is called the “ZE triangle”—which includes the porta hepatis, mid-duodenum, and the head of the pancreas. 80% are of the sporadic form; 20% are associated with MEN Type I.

Consider ZES in patients with:

- Severe esophagitis and chronic diarrhea
- Ulcer (especially duodenal ulcer) and chronic diarrhea
- Duodenal ulcer and big folds in the stomach (from parietal cell hyperplasia)
- Recurrent ulcers and no other risk factors
- Recurrent complicated ulcers
- Post-bulbar duodenal ulcers

To evaluate ZES, first order a serum gastrin while patient is off PPI therapy. If the gastrin level is elevated in a patient with gastric acid, workup usually requires abdominal CT, endoscopic ultrasound, and somatostatin receptor imaging.



## Quick Quiz

- Name 3 EGD findings that indicate increased risk for rebleed of a peptic ulcer.
- What is the most common presentation of ZES?
- What is the usual cause of gastric carcinoid?
- Carcinoid may be associated with which skin condition?
- What are the clinical and environmental risk factors for gastric cancer?

Treatment: All patients with newly diagnosed ZES without evidence of metastatic disease warrant surgical exploration. 1/3 will be cured by **resection of the primary tumor**. Even with metastatic disease, treat ZES aggressively with resection of the primary tumor because the mass effect of the tumor tissue can eventually cause problems (obstruction).

A **PPI** is the **drug of choice** for medical treatment of ZES, although the dose is higher than usual and often must be increased with long-term therapy.

Remember: Other conditions associated with an elevated gastrin level are vitiligo, renal failure, hyperthyroidism, and achlorhydria caused by PPI use or chronic Type A gastritis (see [page 1-10](#)). Also remember that persistent high gastrin levels can cause gastric carcinoids. Speaking of which ...

## GASTRIC CARCINOIDS

Gastric carcinoids are rare (0.5% of gastric tumors) and usually caused by **chronic hypergastrinemic states**. The types of carcinoids are based on the causes of the hypergastrinemic state:

- Type 1: **Autoimmune gastritis/pernicious anemia**
- Type 2: **ZES**, when it occurs as part of multiple endocrine neoplasia—MEN I
- Type 3: **Spontaneous** (least often)

Sometimes gastric carcinoids are associated with **vitiligo**.

Gastrin is trophic to the enterochromaffin-like (ECL) cells of the stomach, leading to hyperplasia and occasionally to gastric carcinoids.

Note: The PPI omeprazole has not been shown to cause carcinoids in humans (> 10 years worth of data), although it does increase the circulating gastrin level.

It is unusual for gastric carcinoids to metastasize or to be symptomatic. They are slow growing and **almost never** cause carcinoid syndrome. See [page 1-25](#) for more on carcinoids.

## GASTRIC CANCER

There are **4** significant malignancies of the stomach:

- 1) **Carcinoids** (just discussed)
- 2) **Adenocarcinoma** (**most common**—95%!)
- 3) **Lymphoma**
- 4) **GIST** (gastrointestinal stromal tumors; e.g., leiomyosarcoma)

There are 2 distinct forms of gastric adenocarcinoma: a **proximal diffuse** type and a **distal intestinal** type. The incidence of distal gastric cancer had been decreasing until about 20 years ago; since then, its incidence has been holding steady. The proximal type has been steadily increasing. See [Image 1-11](#).

The risk factors and associations with gastric cancer include:

- Chronic *H. pylori* infection
- Metaplastic (chronic) atrophic gastritis
- Ménétrier disease (= large stomach folds from epithelial cell hyperplasia)
- Adenomatous gastric polyps (rare)

It appears that **distal** gastric cancer is most strongly associated with **environmental** factors, especially:

- A diet low in fruits and vegetables and high in dried, smoked, and salted foods
- Foods rich in nitrates and nitrites (animal studies)

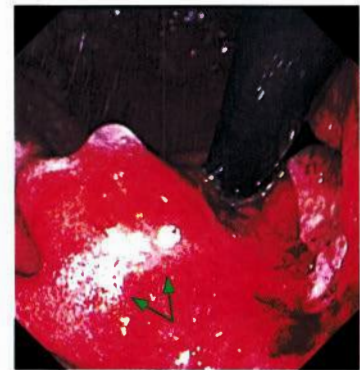


Image 1-11: Gastric adenocarcinoma

Acanthosis nigricans is a reactive skin condition with velvety dark plaques in the intertriginous areas (def: where opposing skin surfaces touch and rub). It is usually due to obesity, but it is also associated with various GI and lung malignancies and conditions that cause insulin resistance. Of the malignancies, **acanthosis nigricans** is most often associated with **gastric cancer**.

Note with *H. pylori* infection—some patients may develop MALT (extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue ... er, like I said, MALT). This is diagnosed by EGD with biopsy. When the *H. pylori* infection is treated, the MALT may resolve. Close endoscopic follow-up is necessary.

Neither **alcohol** consumption nor **gastric ulcers** has been proven to cause gastric cancer—as previously thought—even though gastric cancer can present as an ulcer.

Diagnosis of gastric cancer: Often an ulcer is picked up on EGD or barium contrast study (double contrast is better). If it appears benign, it can be treated. Endoscopy and biopsy are necessary only if the ulcer does not heal.

For a nonhealing ulcer, endoscopy with multiple biopsies is the diagnostic procedure of choice. Tumor markers, such as carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP), are of **no use** as early markers for gastric cancer.

Prognosis is determined by stage (TNM classification), using CT scan and endoscopic ultrasound. Because it is largely asymptomatic until advanced, < 10% are found in the early gastric cancer stage (EGC, confined to the mucosa and submucosa, T1N0M0).

The 5-year survival rate is 85–90% for treated EGC and only 3% for treated invasive, metastatic gastric cancer.

Treatment consists of surgical removal of the cancer and adjacent lymph nodes. Adjuvant combination chemotherapy prolongs survival. Adjuvant radiotherapy is investigational.

## OTHER GASTRIC SYNDROMES

### POSTGASTRECTOMY SYNDROMES

#### Overview

Postgastrectomy syndromes include dumping syndrome, blind loop syndrome, and afferent loop syndrome. All are now infrequent because < 5% of PUD cases warrant surgery.

#### Dumping Syndrome

Dumping syndrome consists of postprandial vasomotor symptoms: **palpitations**, **sweating**, and **lightheadedness**. There are 2 types. The **early** type occurs 30 minutes after eating and is of uncertain etiology. The **late** type occurs 90 minutes or more after eating and is probably due to hypoglycemia. Treat both types identically: Restrict sweets and lactose-containing foods, and encourage frequent small meals.

#### Blind Loop Syndrome

Blind loop syndrome is **bacterial overgrowth** in a loop (usually in patients with prior gastrectomy or Billroth II gastrojejunostomy) manifested by **fat** and **B<sub>12</sub> malabsorption**, and a **low D-xylose absorption test** (bacterial overgrowth and with small bowel mucosal problems).

#### Afferent Loop Syndrome

With a **gastrojejunostomy**, an anastomosis is formed between the stomach and the jejunum. The “afferent

loop” is the portion that was bypassed and through which bile and pancreatic fluids still flow toward the jejunum. Occasionally these patients get “afferent loop syndrome.” Presentation is **abdominal bloating** and **pain** 20 minutes to 1 hour after eating; vomiting often relieves symptoms. The emesis is often bile-colored. Many believe the cause is an incompletely draining afferent loop, which fills with the biliary and pancreatic secretions.

#### Gastroparesis in Diabetics

Highly **variable** gastric emptying is seen in diabetics. Emptying may be slow, normal, or fast. However, long-term diabetics tend to develop **slow** gastric emptying (gastroparesis). This occurs much more commonly in Type 1 than in Type 2.

Blood glucose > 200 mg/dL has been shown to result in decreased antral motility and delayed gastric emptying. Hyperglycemia may also have a negative long-term direct effect on gastric motility.

Conversely, slowed gastric emptying itself tends to increase blood glucose because of the delay of insulinemic and glycemic responses to the carbohydrates. So we have a vicious cycle, and the way to minimize the cycle is to keep tight control of glucose levels.

Clinical presentation is nausea, vomiting, early satiety, and a predisposition for bezoars.

Aside from diabetic neuropathy, gastroparesis can be caused by:

- Autonomic dysfunction—amyloid neuropathy
- An infiltrative process of the smooth muscles—**scleroderma**, amyloidosis
- An antecedent viral infection (particularly norovirus and rotavirus)
- A CNS disorder (stress, MS, parkinsonism, tumor, cord injuries)
- Post-vagotomy
- 1/3 to 1/2 of cases are idiopathic.

Workup of suspected delayed gastric emptying requires that you **rule out** obstruction first. Then diagnosis is **confirmed** with a radioisotope-labeled solid meal.

Treat with:

- good hydration,
- low-fat diet,
- tight control of blood glucose, and
- metoclopramide (**FDA warning**, though, for **long-term use**—extrapyramidal side effects may become permanent!).

IV erythromycin stimulates gastric motility (it is very similar in structure to motilin) but is **less useful** as a long-term therapy—it can be used in the acute setting when oral intake is inhibited by severe stasis.



## Quick Quiz

- What is the relationship of alcohol to gastric cancer?
- How do you rule out gastric cancer in a patient with a nonhealing gastric ulcer?
- How is gastroparesis diagnosed?
- When are barium enemas contraindicated in IBD?
- Sulfasalazine is ineffective in which types of CD?
- What are the side effects of metronidazole?
- When is budesonide used for CD?

## INFLAMMATORY BOWEL DISEASE

### COMMON FACTORS

Inflammatory bowel disease (IBD) comprises **Crohn disease** (CD) and **ulcerative colitis** (UC). In both, family members are at increased risk of IBD, and the patient has an increased risk of GI cancer—but the risk of cancer is much higher in long-standing UC than in CD.

**Toxic megacolon** is a complication in both, so a barium enema is contraindicated if the patient is having an acute exacerbation.

Infectious colitis, early CD, and UC can appear identical on sigmoidoscopy. Stool examination for WBCs, O&P, C&S, and *C. difficile* toxin assay are parts of the initial workup. Refer to [Table 1-2](#) as you review the diagnosis of CD and UC. See [Table 1-3](#) on [page 1-20](#) for a comparison between treatments of CD and UC.

Smoking is associated with both CD and UC, but not in the way you might think. Smokers are more likely

than the normal population to develop CD, but UC is infrequent in smokers (only 10% of UC patients are smokers)!

Colonoscopy is the usual method used to assess IBD. Barium enema is not used anymore, but CT enterography can be helpful in diagnosis of small bowel as well as colonic disease.

The main drugs used to treat IBD include:

- Sulfasalazine
- Mesalamine (5-aminosalicylate or 5-ASA preparations)
- Prednisone
- Budesonide (Crohn disease only)
- Metronidazole
- Azathioprine and its metabolite, 6-mercaptopurine
- Infliximab, adalimumab, and certolizumab (monoclonal antibody to TNF- $\alpha$ )

Methotrexate and cyclosporine are also available.

### COMMON DRUGS FOR IBD

**Mesalamine** (5-aminosalicylic acid, 5-ASA) is normally rapidly absorbed from the upper digestive tract, but different oral formulations release mesalamine into the distal ileum and colon. For colon disease, it is given either rectally—as an enema (proctosigmoiditis) or suppository (for proctitis only)—or in a formulation designed to delay absorption of the drug.

**Sulfasalazine** is split, by bacterial action in the **colon**, into **mesalamine** (active component) and **sulfapyridine**. Because this takes place in the colon, sulfasalazine is **ineffective** for CD of the **small bowel**. The other breakdown product, sulfapyridine, is absorbed in the colon, acetylated in the liver, and excreted in the urine. Sulfapyridine is a highly reactive sulfa moiety, which is responsible for most of the side effects of sulfasalazine—such as reversible infertility in men, leukopenia, and headache.

**Metronidazole** is beneficial for perianal abscesses and fistulas in CD. Combined with a 5-ASA analog, it is useful as maintenance therapy for CD. Long-term use is hampered by the side effect of peripheral sensory neuropathy (particularly if the dose is > 10 mg/kg).

**Budesonide** is an enteric-coated corticosteroid that releases mostly in the ileum and ascending colon. It metabolizes in the liver to inactive products. It has a 90% first-pass effect—thus, much **fewer systemic side effects** than prednisone. It is used specifically for small bowel CD. As with other corticosteroids, bone mineral density should be monitored yearly. At this point, it is uncertain whether budesonide has less effect than prednisone on bone density.

**6-mercaptopurine** (6-MP) and **azathioprine** (which metabolizes to 6-MP) are **prednisone-sparing** drugs

Table 1-2: Comparison of CD and UC

|                         | Crohn Disease         | Ulcerative Colitis            |
|-------------------------|-----------------------|-------------------------------|
| Lesions                 | Focal, skip, deep     | Shallow, continuous           |
| Clinical Course         | Indolent              | More acute                    |
| Prednisone*             | Less responsive       | Very responsive               |
| Granulomas              | Pathognomonic         | None                          |
| Rectal Involvement      | Rectal sparing in 50% | Rectum <b>always</b> involved |
| Perianal Disease        | Abscesses, fistulas   | None                          |
| Small Bowel Involvement | > 50%                 | Backwash ileitis in < 10%     |

\* For flares. Not for long-term maintenance therapy.

useful in both Crohn's and UC, but they usually take **3–4 months** to show an effect. Also, because these 2 drugs have bone marrow suppressive effects, monitor CBC monthly. There is no report of increased malignancy with long-term use of either drug.

**Infliximab** (Remicade<sup>®</sup>), **certolizumab pegol** (Cimzia<sup>®</sup>), and **adalimumab** (Humira<sup>®</sup>) are monoclonal antibodies to **TNF- $\alpha$** . They are given for **moderate-to-severe** Crohn disease, **fistulous** Crohn disease, and **refractory** UC. Know that **TB may reactivate** with usage ... but the **most common** side effect is **URI**.

Note: Monoclonal antibodies (mAb) are immunomodulators that are identical antibodies derived from clones of a single parent cell. The standard recombinant DNA procedure produces mouse (murine) Ab. The human body reacts against these foreign Ab with an inflammatory response. To overcome this, a portion of mouse DNA that codes for the binding site is combined with human DNA. The result is a chimeric (human-murine) Ab or a humanized (mostly human) Ab. The more human, the less reaction. Fully human antibodies have been developed using transgenic mice. Monoclonal Ab's generic names always end in "mab" (mAb, get it?) with the preceding letters further defining what type of antibody it is—chimeric (-ximab), humanized (-zumab), or human (-umab).

Drugs proven to decrease the relapse rate in CD are azathioprine, 6-mercaptopurine, MTX, and also infliximab. (Infliximab reduces relapse only in infliximab-induced remission.) Note that **all** of the standard drugs decrease the relapse rate in UC! Mesalamine drugs and corticosteroids are good for inducing remission in CD but not for maintaining it.

Stopping smoking decreases relapse rate in CD and increases it in UC.

Use in pregnancy:

FDA risk **category B** (no evidence of risk in humans): metronidazole (although generally contraindicated in 1<sup>st</sup> trimester), prednisone, sulfasalazine, and mesalamine.

FDA risk **category C** (risk cannot be ruled out): olsalazine.

## CROHN DISEASE

### Overview

Although most patients present with Crohn disease (regional enteritis) in their **20s or 30s**, the disease **can present at any age**. There is a second, smaller peak of incidence in 70–80-year-olds. The incidence of CD is **increasing**. There is an increased risk of GI cancer with CD, especially with long-standing disease (> 20 years) and Crohn colitis; screen long-term CD patients every other year for cancer.

CD is more **indolent** than UC. Because of this, it is less responsive to treatment, and it is harder to get these patients off steroids. Patients with CD are more likely to have perianal fistulae and abscesses. They are also more likely to have strictures, inflammatory masses, and associated obstruction. One big problem with CD is the **high rate of recurrence**. It was once thought to be 50% at 10 years, but this is the **symptomatic** recurrence rate. Radiologic/endoscopic recurrence rate is 75% at 3 years!

Osteoporosis is common in Crohn disease. About 70% have abnormal bone density—due to chronic disease, vitamin D deficiency, and/or steroids.

### Diagnosis

CD is diagnosed by finding patchy, focal, and aphthous ulcers and deep transmural ulcers (called "Crohn craters"), with occasional strictures and fistula formation. **Granulomas**, infrequently found on biopsy specimen of these ulcers, are pathognomonic. See **Image 1-12** through **Image 1-14**.

A tetrad to remember for "Crohn colitis":

- 1) Rectal sparing
- 2) Skip lesions
- 3) Perianal disease
- 4) Ileocecal involvement

Patients with CD may present with fever, abdominal pain, and systemic symptoms. One classic but uncommon feature is the "**string sign**," which may be seen in the terminal ileum during a small bowel follow-through. The terminal

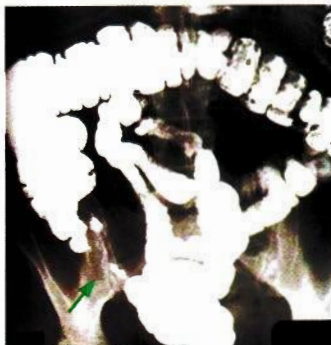


Image 1-12: Crohn colitis with "string sign" in RLQ

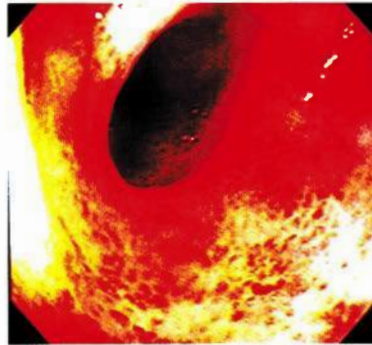


Image 1-13: Crohn proctitis



Image 1-14: Crohn disease with submucosal edema causing cobblestone appearance



## Quick Quiz

- What are the indications for monoclonal antibodies in patients with IBD?
- What is the relationship of Crohn disease to cancer?
- What are the colonoscopy and biopsy findings in Crohn's?
- What is the significance of an "apple-core" lesion in patients with CD? How does it differ from the "string sign"?
- What GU complication can arise in a patient with Crohn's of the terminal ileum?
- What is the usual etiology of diarrhea in CD patients with > 100 cm of distal ileum removed? With < 100 cm of distal ileum removed? What is the treatment for each?

ileum is so edematous and/or fibrotic that the lumen is compressed and shows up as a "string" of contrast. The **edema** pushes the rest of the bowel away so the **string sign** shows up well. If you see this narrowing of the lumen elsewhere in the colon, it is called an **apple-core** lesion, which suggests **cancer**. Bowel involvement in CD: 30% colon only, 40% small bowel only, and 30% both.

Initially, a definitive diagnosis cannot be established in up to 15% of patients with IBD. Serologic tests (p-ANCA and ASCA, anti-saccharomyces antibody) can be useful in indeterminate cases. **p-ANCA** is associated with **UC** and **ASCA** with **CD**.

### Extraintestinal Manifestations of CD

The extraintestinal manifestations occur primarily in CD involving the **colon**. These manifestations are identical to those of UC (which involves **only** the **colon**). So, these are discussed later under Extraintestinal Manifestations of Ulcerative Colitis on [page 1-21](#).

### Terminal Ileum Problems in CD

Problems related to disease/resection of the terminal ileum are found in CD—but **not** in UC. These problems include:

- Calcium oxalate **kidney stones** (if steatorrhea present)
- **Gallstones**
- **B<sub>12</sub> deficiency**
- **Hypocalcemia** (from vitamin D malabsorption)
- Bile acid-induced **diarrhea**
- Nutrient **malabsorption**

What type of gallstones occurs? Probably not what you think. Previously, it was thought that cholesterol

gallstones formed in this situation because of the loss of bile salts and that the resulting bile became supersaturated with cholesterol. But now it appears that this is probably not the case. **Pigment** gallstones are the usual type, and the risk appears to correlate with the amount of ileal disease or resection.

Note that anytime **> 60 cm** of terminal ileum is resected, patients have **B<sub>12</sub> malabsorption**.

Bile acid-induced diarrhea is usually the cause of diarrhea in Crohn patients when **< 100 cm** of distal ileum is resected. Some of the bile acids **escape absorption** in the terminal ileum and go on to stimulate colonic salt and H<sub>2</sub>O secretion by the colon. Treat with **bile acid sequestrants** (e.g., cholestyramine, colestipol), which bind and inactivate the bile acids.

When **> 100 cm** of distal ileum is resected, the patient gets **steatorrhea** from greatly **decreased** proximal gut concentration of bile salts (synthesis does not keep up with GI loss with the loss of distal ileum resorption). Treat these patients with a **low-fat diet**. Sometimes, the low-fat diet does not allow them to get enough calories. In this case, give them supplemental medium-chain triglycerides (MCT).

### Treatment Overview for CD

Medical treatment of CD uses many of the same drugs as that for UC. See more detail on these medications on [page 1-20](#).

Medical treatment of CD:

- 5-aminosalicylate (5-ASA, mesalamine—slow-release formulations)
- Olsalazine
- Corticosteroids (prednisone, budesonide)
- Infliximab (Remicade®)
- Metronidazole
- Ciprofloxacin
- Azathioprine (and its metabolite, 6-mercaptopurine)

Know [Table 1-3](#) on next page. And know:

- In general, treatment for **mild** disease is a slow-release oral **5-ASA formulation** with progression to other drugs if response is not adequate. 5-ASA analogs are more effective in CD with **colon** disease only vs. ileal or ileocolic disease.
- **Prednisone** is more effective in **UC** than CD—again, probably due to the **indolent** nature of CD. In CD, prednisone is more effective than sulfasalazine when CD affects only the small intestine. Prednisone is best used **only** for **flares**; long-term use (> 3 months) should be discouraged because of side effects.
- **Budesonide** is a 2<sup>nd</sup> line drug for mild-to-moderate CD localized to the ileum.
- **Infliximab** (Remicade®) is helpful in patients with fistulas, and it also facilitates withdrawal from corticosteroids. Before starting this agent (or adalimumab,

below), **screen** all patients for **tuberculosis**. The most common adverse reactions are development of a **positive ANA** in 55% and URIs in 32%. **Severe fungal infections**, in addition to tuberculosis, can be seen while on therapy. Additionally, **lymphoma** and **multiple sclerosis** have been described.

- **Metronidazole** is effective, especially for fistulas and perianal CD (used for UC only when there is fulminant disease with peritonitis). Combined with a 5-ASA analog, it is useful as maintenance therapy for CD. Again, long-term use is hampered by **neuropathy**.
- **Ciprofloxacin** is also occasionally used for fistulous or perianal Crohn disease.
- **6-mercaptopurine (6-MP)** and azathioprine are used with Crohn patients who cannot be weaned off prednisone. Note: Long-term treatment with 6-MP and azathioprine has been shown to decrease recurrence rates in CD.

Like 6-MP and azathioprine, mesalamine also probably decreases the relapse rate in CD. Prednisone and metronidazole do not affect relapse rate.

### Surgery and Recurrence in CD

Surgery is only for intractable disease and specific serious complications. Previously, 60% of Crohn patients required surgery in the first 5 years and then again after ~ 8 years. These numbers are decreasing with medical therapy (especially 6-MP, infliximab).

The incidence of **recurrence after surgery** depends on:

- Site—ileocolic is highest.
- Nature of the complication—obstruction, perforation, and abscess have higher incidence and rates of recurrence.

Essentially, the worse the disease is where you cut, the more likely is the recurrence at that site. Colectomy and ileostomy provide the best results for Crohn colitis when there is **no ileal** inflammation (> 60% have no recurrence).

### Treatment Scenarios for CD

**Colon only:** sulfasalazine or mesalamine tablets/enemas. Sulfasalazine is about \$30/mo vs. \$300+/mo for mesalamine and other drugs. Therefore, sulfasalazine is the

**Table 1-3: Tx of Inflammatory Bowel Disease. Comparison of Treatments Used in Ulcerative Colitis and Crohn Disease**

| Ulcerative Colitis                   |               |                                                                                                                                   |                                                                                                                  |                                                                                                           |                                                                                     |                                                                                                                                                          |
|--------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Severity:                            |               | Mild                                                                                                                              | Moderate                                                                                                         | Severe                                                                                                    | Fulminant                                                                           | Remission                                                                                                                                                |
| ... definition of severity           | Stools/d      | < 4                                                                                                                               | Between mild and severe                                                                                          | > 6                                                                                                       | > 10                                                                                | Normal                                                                                                                                                   |
|                                      | KUB           | Normal                                                                                                                            |                                                                                                                  | Air, edema, thumbprinting                                                                                 | Bowel dilation                                                                      |                                                                                                                                                          |
|                                      | Physical exam | Normal; but h/o intermittent fecal blood                                                                                          |                                                                                                                  | Fever, Abd tenderness, freq fecal blood                                                                   | Fever, Abd tenderness, and distention                                               |                                                                                                                                                          |
| Treatment:                           |               | Distal disease:<br>Rectal corticosteroids; oral or rectal aminosaliclates<br>Extensive colon involvement:<br>Oral aminosaliclates |                                                                                                                  | Distal disease:<br>Oral or rectal corticosteroids<br>Extensive colon involvement:<br>Oral corticosteroids | IV corticosteroids<br>IV cyclosporine or infliximab if resistant to corticosteroids | Oral aminosaliclates (rectal okay if distal disease)<br>Oral azathioprine or mercaptopurine if steroid dependent or refractory                           |
| Crohn Disease                        |               |                                                                                                                                   |                                                                                                                  |                                                                                                           |                                                                                     |                                                                                                                                                          |
| Severity: Definitions same as for UC |               | Mild                                                                                                                              | Moderate                                                                                                         | Severe/Fulminant                                                                                          | Post-Op                                                                             | Remission                                                                                                                                                |
| Treatment:                           |               | Oral aminosaliclates; metronidazole                                                                                               | Oral corticosteroids (short term < 3 months); azathioprine, 6-MP, or methotrexate if steroid depdt or refractory | IV corticosteroids; IV infliximab; Elemental diet or TPN = transient benefit                              | Metronidazole (delays anastomotic recurrence — danger of neuropathy)                | Oral aminosaliclate; azathioprine or 6-MP especially if steroid dependent or refractory; Note: 6-MP or azathioprine is now standard maintenance therapy. |

Note the differences and similarities in these treatments! Metronidazole and diet (bowel rest) are ineffective in UC. Rectal preparations are used only in UC of the **distal** colon.



## Quick Quiz

- What additional screening should be done in patients with Crohn's who have been treated with chronic steroids?
- What are the findings of UC on colonoscopy?
- What serological marker may be found in 70–80% of patients with UC?
- Describe the extraintestinal manifestations of UC.

first choice—then 5-ASA drugs, if required because of intolerance to the side effects of sulfasalazine.

**Any ileum or small bowel** involvement: slow-release mesalamine.

**Only ileum or small bowel** involvement: slow-release mesalamine or budesonide.

**Fistula or perianal**: infliximab (or other immunomodulators), metronidazole, or ciprofloxacin. 6-MP also used.

Steroid-dependent: 6-MP, azathioprine, mAb.

Corticosteroids are a first-line drug for incomplete acute small bowel obstruction. Otherwise, they are used for flares and only if there is inadequate response to the 5-ASA drugs.

Note: Be sure to screen CD patients for **osteoporosis**. About 70% have abnormal bone density due to chronic disease and/or steroids.

## ULCERATIVE COLITIS

### Overview

Ulcerative colitis (UC) consists of uniform, **continuous** mucosal inflammation with **shallow** ulcers that **always** start in the rectum and extend proximally (**Image 1-15**). There is usually a sharp margin between the area of involvement and the normal mucosa. The area of involvement **tends** to remain the same from the time of diagnosis but does extend more proximally in 10%.

70–80% of UC patients are **p-ANCA**-positive, although this test is of little use clinically (low sensitivity and specificity). ESR and C-reactive protein (CRP) are often elevated.

The main symptoms of UC are abdominal pain and bloody diarrhea. Clinical course and degree of involvement are variable—from mild ulcerative proctitis (rectal area only) with minimal symptoms to severe colitis of the entire colon with bad cramps,

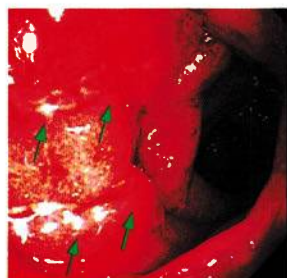


Image 1-15: Ulcerative colitis

liquid stools containing blood and pus, anemia, extraintestinal manifestations (below), and constitutional symptoms. Occasionally, tenesmus (painful anal sphincter spasm with no bowel movement) and constipation may be the major clinical presentation.

You must rule out **infectious** causes of colitis:

- *E. coli* O157:H7 (EHEC)
- *Shigella*
- *Salmonella*
- *Yersinia*
- *Campylobacter*
- *C. difficile*
- *E. histolytica* (amebiasis)

Especially *Campylobacter*—since it can have a chronic, relapsing course that mimics UC.

Consider *C. difficile* infection in a **flare-up**—it is usually thought of as an acute disease, but it can manifest as diarrhea 1–3 months after antibiotic use! Don't forget that *C. difficile* can occur even without antibiotic use.

Diagnosis is made with colonoscopy or sigmoidoscopy.

### Extraintestinal Manifestations of UC

Extraintestinal manifestations of IBD are usually seen in IBD patients with **colitis** (so they are usually associated with UC, although they can be seen in CD involving the colon).

“**JSEM**” is the mnemonic for diseases seen with colonic disease (colitis): **Joint, Skin, Eyes, and Mouth**. These extraintestinal manifestations of UC include:

- Skin lesions—*E. nodosum* and pyoderma gangrenosum—which correlate with disease activity
- RF-negative peripheral polyarthritis
- Iritis/episcleritis/uveitis (HLA-B27+)
- Venous thrombosis
- Ankylosing spondylitis (also HLA-B27+)
- Pericholangitis
- Primary sclerosing cholangitis (PSC, HLA-B8+, see [page 1-46](#))

The complications associated with HLA antigens **tend not** to improve with improvement of colitis, whereas the other problems mentioned here usually get better as colitis improves!

So, what disease do you think of if a patient with UC develops jaundice, itching, and cholestatic LFTs?

Note that the JSEM mnemonic leaves out primary **sclerosing cholangitis**, the answer to this question! PSC occurs in 5% of UC patients. As with any newly increased LFTs, do an ultrasound first, then do MRCP (shows “string of beads”, multifocal strictures of intrahepatic bile ducts) to confirm the diagnosis of PSC.

Check LFTs, especially alkaline phosphatase, initially and periodically. If the alk phos becomes **2 x nl** and **persists**, work up for **sclerosing cholangitis**.

## Cancer in UC

Risk of cancer in patients with UC is high. Risk starts increasing about 8 years after onset of symptoms. It is up to 10% at 20 years and up to 20% at 30 years. Risk increases with the following:

- Duration of UC
- Extent of UC—pancolitis has the highest risk, whereas ulcerative proctitis has no increased risk
- Concurrent PSC
- Persistent mucosal inflammation (disease activity)
- Dysplasia

Any patient who has had UC for **10 years** should have a colonoscopy with multiple biopsy samples to check for dysplasia. Once started, routine colonoscopy screening for cancer every 1–3 years should be continued.

## Treatment of UC

UC is **cured** with surgery! But it may be difficult surgery, so reserve it for findings of cancer or dysplasia! UC colectomy is recommended for patients with dysplasia in a mass lesion and for high-grade dysplasia in flat mucosa. Repeat colonoscopy in 6 months if there is low-grade dysplasia **without** inflammation. Some authorities recommend colectomy if low-grade dysplasia without inflammation is confirmed on 2 biopsies within 6 months. Repeat in 6–12 months for dysplasia with inflammation (usually not precancerous).

Other indications for UC surgery besides cancer are:

- Intractable disease
- Perforation
- Growth retardation in children
- Toxic megacolon
- Stricture
- Steroid dependence
- Exsanguinating hemorrhage
- Complication from therapy

Know all the treatments for UC! Therapy for UC is changing due to the advent of 5-ASA compounds without sulfa, newer immunomodulators, and short-term use of corticosteroids. UC, a more acute inflammatory process, responds to steroids much better than CD (Table 1-3).

For **mild disease**, there are several options:

- Oral sulfasalazine
- Oral mesalamine
- Rectal mesalamine (suppository for proctitis; enema for proctosigmoiditis)
- Hydrocortisone enemas

All have similar efficacy—75% response and 30% remission after 2 months. The HC enemas have few side effects and give quicker symptom relief than mesalamine.

For **moderate-to-severe** UC, initial therapy is oral prednisone. Hospitalize patients with fulminant UC and treat with IV corticosteroids, infliximab, or cyclosporine; the patient may need a colectomy if fulminant symptoms persist for > 48 hours.

**Maintenance** therapy after remission:

- Sulfasalazine or mesalamine daily for 2 or more years.
- Azathioprine and 6-mercaptopurine for frequent recurrences/steroid dependence; treatment may take **3–4** months to show an effect.
- Cyclosporine provides short-term remission in 40–50% of patients with severe colitis, but long-term remission in only 20–30%.

A few buzzwords:

- Tenesmus (UC)
- Rectal bleeding (UC)
- Fecal soiling (think fistula = CD)
- Hydronephrosis without stones (obstruction from inflammatory mass = CD)
- Pneumaturia (think fistula to the bladder = CD)

# DIARRHEA

## OVERVIEW

Diarrhea is defined variably as **> 200–250 g/day** of stool. Normal average daily output is **150–180 grams**. Note: Small-volume, loose stools are not considered diarrhea. Normal bowel frequency varies from 3 to 21 stools/week.

Diarrhea is typically categorized by duration of symptoms. Acute is < 2 weeks, persistent is 2–4 weeks, and chronic is > 1 month.

## ACUTE DIARRHEA

The infectious causes of acute diarrhea are covered in the Infectious Disease section, Book 1, under Common ID Syndromes: Gastrointestinal.

## Introduction

Acute diarrhea is usually of an **infectious** etiology, but it may also be caused by food poisoning or drug side effects. Infectious diarrhea may be invasive or noninvasive.

## Diagnosis of Acute Diarrhea

Do the simple things first! Check diet and travel history.

Lab: First, check fecal WBCs. The invasive types usually are positive for fecal WBCs.



## Quick Quiz

- What is the relationship of UC to cancer?
- What is the treatment for UC with high-grade dysplasia
- What is the treatment for moderate-to-severe UC?
- Associate these “buzzwords” with UC or CD: a) tenesmus, b) rectal bleeding, c) fecal soiling, d) pneumaturia.
- How is diarrhea classified?
- What tests are done for the workup of acute diarrhea?
- What are the treatments generally used for invasive diarrhea?
- Which cause of invasive diarrhea should not be treated with antibiotics?

If these are elevated, do:

- Culture + Sensitivity exam (C+S)
- Ova + parasite exam (O+P) (especially with positive travel history)
- +/- sigmoidoscopy with biopsy

If you suspect *E. coli* O157:H7 (enterohemorrhagic *E. coli*; EHEC), specifically ask for MacConkey-sorbitol agar for the stool culture media. If you suspect *Clostridium difficile*, also add *C. difficile* toxin assay.

Rectal/colonic biopsies can be useful in differentiating infectious colitis from inflammatory bowel disease. Crypt abscesses may be found in both, but crypt distortions are found **only** in inflammatory bowel disease.

### Treatment of Acute Diarrhea

Generally, **invasive** diarrhea is treated with TMP/SMX, but use macrolides for *Campylobacter* and metronidazole for amebiasis. Antibiotics may **prolong** *Salmonella* infections and therefore are usually not used. Quinolones (especially ciprofloxacin) are effective in all of these, except *Campylobacter* (resistance by *Campylobacter* to quinolones is too high to use them empirically) and amebiasis, and are an alternative 1<sup>st</sup> choice.

Another **big** exception is *E. coli* O157:H7 infection (EHEC), which is treated only symptomatically; antibiotics are **contraindicated**!

Before reading further, go to the Infectious Disease section, Book 1, to review more detail on the specific organisms and treatments.

## CHRONIC DIARRHEA

### Mechanisms of Chronic Diarrhea

#### Overview

Again, chronic diarrhea is defined as loose stools > 200–250 g/day for > 1 month.

Chronic diarrhea can be classified according to 3 mechanisms: **osmotic**, **secretory**, and **increased motility**. First, we will compare and contrast osmotic and secretory mechanisms. In this section, when discussing ion concentrations, note that “[x]” means “concentration of x.”

In normal bowel contents, the cations are equal to the anions:

$$[\text{Na}^+] + [\text{K}^+] = [\text{Cl}^-] + [\text{HCO}_3^-] + \text{other anions}$$

(The “other anions” are mostly short-chained fatty acids that are usually absorbed early in bowel transit.)

So you can calculate stool osmolality using only the  $\text{Na}^+$  and  $\text{K}^+$  concentrations:

$$\text{Stool osmolality}_{\text{calc}} = 2[\text{Na}^+ + \text{K}^+]$$

For normal stool and for diarrhea of any cause:

$$\text{Stool osmolality} = \text{serum osmolality}$$

But! ... Depending on the cause of the diarrhea, the amount of **unmeasured** anions may vary from normal to high.

Note: Serum osmolality is typically 280–300 mOsm/L—or, for the equations, 290 mOsm/L.

Because the fluid in **secretory** diarrhea is, in essence, an ultrafiltrate of the serum, secretory diarrhea is similar to normal stool in that  $2[\text{Na}^+ + \text{K}^+] = 290 \text{ mOsm/L}$ .

With **osmotic** diarrhea, part of the osmolality is due to unmeasured, nonabsorbable, osmotically active molecules—so the  $2[\text{Na}^+ + \text{K}^+]$  is much less than 290 mOsm/L. This difference is usually > 50 mOsm/L.

Summary: Here are the pertinent equations again. Learn them, and you should be able to handle this topic:

$$\text{Stool Osm}_{\text{calc}} = 2 \times (\text{stool } [\text{Na}^+] + \text{stool } [\text{K}^+])$$

$$\text{Stool Osmolar Gap} = 290 - \text{Stool Osm}_{\text{calc}}$$

If **SOG > 50**, the gap is increased, and added osmoles are present that are causing diarrhea.

When the **SOG < 25**, the stool is either normal, or the diarrhea is secretory.

These calculations are very academic and work in straightforward situations, but **many** causes of diarrhea have **both** secretory and osmotic components. At the bedside, the calculations are less useful. For a Board exam, though, definitely know how to do this.

Make sure this makes sense to you before you move on!

**Table 1-4: Osmotic vs. Secretory Diarrhea**

|                                             | Osmotic         | Secretory       |
|---------------------------------------------|-----------------|-----------------|
| Volume/day                                  | < 1 L           | > 1 L           |
| Effect of Fasting on Diarrhea               | Decreases > 50% | Decreases < 20% |
| Serum (= Total Stool) Osmolality            | 290             | 290             |
| Example [Na <sup>+</sup> ]                  | 40              | 105             |
| Example [K <sup>+</sup> ]                   | 20              | 40              |
| So [Na <sup>+</sup> ] + [K <sup>+</sup> ] = | 60              | 145             |
| 2([Na <sup>+</sup> ] + [K <sup>+</sup> ])   | 120             | 290             |
| Osmotic Gap                                 | > 50            | < 50            |

**Secretory Diarrhea**

In **secretory** diarrhea,  $2[\text{Na}^+ + \text{K}^+]$  of the stool = 290 mOsm/L; i.e., measured serum osmolality. There is more stool volume in secretory diarrhea than in osmotic diarrhea, often > 1 L/d, so there is obviously an increased secretion of electrolytes; thus the patient is at risk for an **electrolyte deficiency**.

There are many causes of secretory diarrhea:

- Enterotoxins from *E. coli*, cholera, and *S. aureus*
- Villous adenomas
- Gastrinomas
- Microscopic colitis
- Collagenous colitis
- Bile acids
- VIPomas that produce vasoactive intestinal peptide (VIP)

A 24–48 hour fast does **not** decrease secretory diarrhea, **except** in fatty acid- and bile acid-related diarrheas.

See Table 1-4.

**Osmotic Diarrhea**

In **osmotic** diarrhea,  $([290] - 2[\text{Na}^+ + \text{K}^+])$  is > 50. So, there is at least a 50 mOsm/L osmotic gap that is due to a nonabsorbable osmotic agent. A 24-hour fast **does** resolve or greatly improve the diarrhea. Lactase deficiency is one of the **most common** causes of osmotic diarrhea. Other common causes are: Mg-containing laxatives and antacids, non- or poorly absorbable carbohydrates (xylitol, lactulose, sorbitol, fructose), and nutrient malabsorption; i.e., pancreatic insufficiency, celiac disease, bacterial overgrowth. If an osmotic diarrhea persists despite a 24-hour fast, suspect surreptitious ingestion of an Mg-containing antacid. Most laxatives, including castor oil, cause an osmotic diarrhea.

**Diarrhea 2° Increased Motility**

Increased motility: The last mechanism of diarrhea is increased motility. The **dysmotility** syndromes include antibiotic-associated diarrhea, hyperthyroidism, carcinoid, and irritable bowel. Erythromycin is one of the most common causes of antibiotic-associated diarrhea. It binds to motilin receptors, thereby increasing bowel **motility**. Treatment for most antibiotic-associated diarrhea is to stop the drug. Antibiotic-associated **colitis** is a different animal (*C. difficile*, discussed later).

Different mechanisms of diarrhea may occur together in certain diseases. In **celiac** disease, osmotic and secretory mechanisms coexist because there is malabsorption of carbohydrates (osmotic) and fat (secretory). **Exudative** diarrhea (i.e., high fecal WBCs; includes invasive bacteria and IBD) contains all 3 mechanisms: Inflammation causes altered motility, and malabsorption can cause both osmotic and secretory components.

**Causes of Chronic Diarrhea****AIDS**

[Know!] 60% of AIDS patients have diarrhea and weight loss. If the patient with AIDS has diarrhea and weight loss **without fever but has a low CD4 count**, suspect one of these noninvasive organisms: *Cryptosporidia* (usual cause), *E. histolytica*, *Giardia*, *Isospora*, *Strongyloides*, or AIDS enteropathy.

**With fever**, think *Mycobacterium*, *Campylobacter*, *Salmonella*, *Cryptococcus*, *Histoplasma*, and CMV. (These are covered in the Infectious Disease section, Book 1, under Common ID Syndromes: Gastrointestinal.)

**Volume** is a big clue in AIDS-associated diarrhea; > 1 L/d suggests a small bowel cause.

A CD4 count < 200, especially if accompanied by weight loss, points to an infectious etiology rather than AIDS enteropathy.

**IBD**

[Know!] Chronic inflammatory diseases of the **colon** (UC and Crohn colitis) cause loose stools with **many** WBCs and histologic damage. Volume may be greater or less than 200 g/day. Chronic bloody stools suggest UC. Chronic loose stools associated with chronic RLQ abdominal cramping, especially palpation of thickened bowel in the RLQ, suggest CD.

Note: **Fecal WBCs and blood** are found in **both** invasive diarrhea and UC. See page 1-17 for more on IBD.

**Diabetes**

Diabetic diarrhea may be caused by:

- Use of dietetic foods rich in **sorbitol** (erroneously labeled “sugarless”)



## Quick Quiz

- What is the osmolar gap in patients with osmotic diarrhea?
- Will a 24-hour fast stop osmotic diarrhea?
- In an AIDS patient with fever and diarrhea, what organisms are on your differential list?
- What is the clinical presentation of carcinoid syndrome?
- What tumor causes the majority of cases of carcinoid syndrome?
- How do you diagnose carcinoid?
- Visceral autonomic neuropathy (Especially suspect this in the **incontinent** diabetic patient.)
- Malabsorption (less common) due to celiac disease (present in 5% of diabetics), pancreatic insufficiency, or bacterial overgrowth (treat with metronidazole and amoxicillin-clavulanate)
- Pancreatic exocrine insufficiency (more common in DM due to pancreatic disease)

### Carbohydrate Intolerance

Consider carbohydrate intolerance in all patients with chronic diarrhea who excessively ingest beverages rich in sorbitol and fructose. Note: Coke/Pepsi has 40 gm of fructose per 16 oz (480 mL).

### Carcinoid

There are several types of carcinoid tumors (**GI, lungs, kidneys, ovaries**), and they can present with **carcinoid syndrome** or symptoms associated with **tumor growth**, such as pain or obstruction.

**Carcinoid syndrome** is the neuroendocrine manifestation caused by release of vasoactive mediators, including 5-hydroxytryptophan, 5-hydroxytryptamine, histamine, kallikrein, and prostaglandins.

With GI tumors, carcinoid syndrome occurs only when the primary tumor has metastasized to the liver. In other tumors, the liver deactivates the vasoactive mediators, so symptoms don't occur. But, with liver mets, the vasoactive mediators are released directly into the circulation from the liver and, thus, aren't deactivated. Some bronchial carcinoids can present with carcinoid syndrome, but it's rare, rare, rare.

So, when you see carcinoid syndrome, think **GI primary** with **hepatic metastases**! Then think, rarely a **bronchial carcinoid** will do this.

Most carcinoids are asymptomatic, are found in the GI track outside of the midgut, and do not metastasize. Most symptomatic carcinoids are associated with a primary tumor in the midgut (ileum and proximal colon).

Carcinoid is an uncommon cause of chronic diarrhea. Gastric carcinoids are related to hypergastrinemic states (this aspect is discussed on [page 1-15](#)).

Carcinoid syndrome presents as **paroxysmal flushing**; crampy, explosive **diarrhea**; and **hypotensive tachycardia**. The flushing is often bright red to violaceous, with well-defined borders, and can be on the whole body—including palms and soles.

Because tryptophan, a precursor of niacin, is used up in carcinoid syndrome, **niacin deficiency** (pellagra) may occur (scaly rash, thickened tongue, angular cheilitis, and mental status changes).

Diagnosis of carcinoid: Check 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA)—a breakdown product of 5-hydroxytryptamine. Normal is less than 10 mg/d; with carcinoid, patient has > 25 mg/d. In patients with carcinoid syndrome from a primary GI tumor, CT of liver should show metastatic lesions.

### Visceral Autonomic Neuropathy (Diabetes, Amyloidosis)

Visceral autonomic neuropathy is characterized by:

- Delayed gastric emptying (i.e., gastroparesis)
- Postural decrease in blood pressure
- Anhidrosis (inability to tolerate heat, lack of functioning sweat glands)—especially in **lower** extremities
- Fecal incontinence
- Impotence (men)
- Urinary overflow incontinence

Patients may exhibit any one or all of the above!

### Microscopic Colitis

Microscopic colitis consists of both **collagenous** colitis and **lymphocytic** colitis. These patients have normal-looking mucosa but abnormal findings on mucosa biopsy (hence the name microscopic colitis). These patients have a chronic secretory, watery diarrhea.

Colonoscopy is normal, but wall biopsy of the normal-looking mucosa shows a lymphocytic infiltrate or a collagenous band in the submucosa. Know: These entities do **not** progress to IBD.

### Other

Other causes of chronic diarrhea include:

- Steatorrhea (discussed further below)
- Endocrinopathies (hyper- and hypothyroidism, adrenal insufficiency)
- Colon cancer
- Radiation-induced disease
- Fecal incontinence (radiation; diabetes; rectal surgery; and childbirth injury to anal sphincter, especially forceps delivery)

Patients may not want to mention that they have fecal incontinence. They frequently will get around the issue by asking “for medication to control the diarrhea.” Ask patients with diarrhea if they experience fecal incontinence more than once a week. If so, the differential diagnosis includes the items listed previously.

### Chronic Loose Stools

The following may cause loose stools < 200 g/day, so do **not** meet the criteria of diarrhea:

- Lactase deficiency (lactose intolerance) is a common cause of loose stools, although the volume is usually < 200 g/day.
- Irritable bowel syndrome (IBS) has loose stools with normal daily volume. See [page 1-30](#) for more on IBS.

### Diagnosis of Chronic Diarrhea

As soon as you make the diagnosis of chronic diarrhea, **stop** testing. Know the following 3 stages:

#### Stage 1

- Stool O&P
- Fecal leukocytes x 3
- Serum chemistry, thyroid profile, and gastrin level
- *C. difficile* toxin assay
- Stool pH
- Weight of stool/d.
- 3-day fecal fat (or if Sudan stain is positive, do the fecal fat)
- Lactose-free diet if lactase deficiency is at all suggested by history

#### Stage 2

- Immunoabsorbent assay for giardiasis
- If **steatorrhea** is confirmed, order ultrasound or CT scan for pancreatic calcification (discussed in detail shortly).
- If **diabetic** has suggestive history: Do either a lactulose breath test for bacterial overgrowth or (more often) just treat empirically.
- If > 1,000 cc/d of stool, check vasoactive intestinal polypeptide.
- Check for laxative abuse by:
  - Specific urine tests for bisacodyl, anthraquinones, and phenolphthalein
  - Stool osmotic gap > 100 mOsm/L (magnesium-containing)
  - Stool measurement of phosphate and sulfate
- If the stool osmolality is < 290, the patient could be adding water or urine to the stool.
- Also may do sigmoidoscopy and high-quality UGI

#### Stage 3

- EGD and colonoscopy

A significant number of patients have no discernible cause of the diarrhea and have no abdominal pain and normal EGD and colonoscopy. These patients have **idiopathic chronic diarrhea**.

Often, a hospital stay is required after stage 3 to redo the previous tests with better controls. Suspect occult bile acid diarrhea if the patient has no abdominal pain and loose watery stool.

### Loose Stools and Fecal Impaction

Watery stool will leak around a fecal impaction, causing small-volume watery effluent. See more on fecal impaction on [page 1-38](#).

## MALABSORPTION

### Overview

Malabsorption may be short-lived, but patients often present with **chronic diarrhea**.

The “**Big 6**” blood tests are those done in the routine workup for malabsorption. These tests are albumin, Ca<sup>++</sup>, cholesterol, carotene, serum iron (all **low**), and PT (**prolonged**).

These are discussed a little later in this section, but first we will discuss the causes of malabsorption—which can be divided into decreased **mucosal transport** (something wrong with intestinal uptake) or decreased **digestion** (not enough digestive enzymes).

### Malabsorption Due to Decreased Mucosal Transport

#### Introduction

Decreased mucosal transport may be caused by celiac disease, tropical sprue, common variable immune deficiency with hypogammaglobulinemia, Whipple disease, intestinal lymphoma, eosinophilic gastroenteritis, bacterial overgrowth, and other small bowel disease. These are discussed below.

#### Celiac Disease

Celiac disease (gluten-sensitive enteropathy, previously celiac sprue, nontropical sprue) is one of the most commonly undiagnosed disorders. It occurs in up to 1% of the population of most countries. Gluten is in wheat, barley, malt, and rye.

Celiac disease is an autoimmune intestinal disorder in which there is an altered gut mucosal response to dietary gluten, resulting in small bowel villous atrophy and crypt hypertrophy with resulting malabsorption. It can cause **growth retardation** and is associated with HLA-DQ2 and HLA-DQ8. It may go into remission during adolescence, then recur. If detected **early**, the patient may have mild symptoms such as **bloating** and **loose stools**.



## Quick Quiz

- Explain each of the 3 stages used in the workup of chronic diarrhea.
- What lab tests are done in the workup of malabsorption?
- What are the extraintestinal manifestations of celiac disease?
- How do you diagnose celiac disease?

### Extraintestinal manifestations of celiac disease:

- Iron deficiency anemia (most common presentation; iron is absorbed mostly in the duodenum): low Hgb, MCV, and ferritin
- Abnormal serum aminotransferases
- Dermatitis herpetiformis—discussed below
- Osteoporosis
- Osteomalacia
- Neuropsychiatric symptoms
- Dental enamel defects

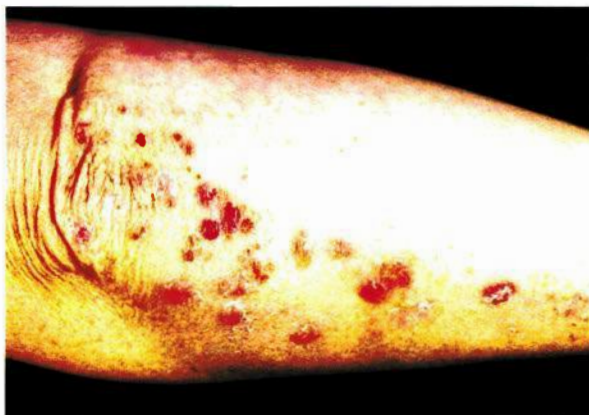
Primary intestinal lymphoma is a rare, late complication of celiac disease.

### Deficiencies caused by celiac disease:

- Iron
- Folic acid
- Calcium
- Vitamin D
- Vitamin B<sub>12</sub> (rarely)

There is a wide spectrum of presentations. Patients often have little or no GI symptoms and may present with only a psychiatric disorder, osteomalacia, or a purulent pustular rash.

Dermatitis herpetiformis is a manifestation of celiac disease in which there are vesiculopapular eruptions on the face, trunk, buttocks, sacrum, and extensor surfaces of elbows and knees (*Image 1-16*).



*Image 1-16: Dermatitis herpetiformis*

Most patients with dermatitis herpetiformis do not have abdominal symptoms, although 85% have the characteristic findings on intestinal wall biopsy.

Diagnosis of celiac disease has the following 4 requirements:

- 1) Evidence of **malabsorption** (steatorrhea, weight loss, iron deficiency anemia)
- 2) Usually a positive tissue **transglutaminase** antibody test (90+% sensitivity) or positive **antiendomysial** antibody test
- 3) A positive **response** to a gluten-free diet (clinical, chemical, and histological)
- 4) Abnormal small bowel **biopsy** to clinch the diagnosis

The best antibody tests are:

- Tissue transglutaminase (tTG) antibody
- IgA antiendomysial Ab

Antigliadin antibodies (AGA) are sensitive but not specific and are superseded by tTG antibody or antiendomysial Ab. Because IgA deficiency occurs in 1–2% of U.S. population, if IgA tTG antibody is negative with strong suspicion of sprue, check serum IgA levels. These antibody tests may also be useful for determining **latent** celiac disease or as a measure of compliance with the gluten-free diet.

Note: The small bowel biopsy results are characteristic but not pathognomonic, since you may see similar villous atrophy with hypogammaglobulinemia (“hypogammaglobulinemic sprue”), small intestinal bacterial overgrowth, lactose intolerance, giardiasis, peptic duodenitis, and tropical sprue! Many small bowel disease processes can cause villous atrophy.

Treat celiac disease with a **gluten-free diet** (GFD). 80% eventually respond. For those patients who do **not**, consider:

- Noncompliance
- Intestinal lymphoma
- Microscopic colitis
- T-cell enteropathy
- Lactose intolerance 2° lactase deficiency (damaged mucosa)
- Pancreatic insufficiency
- Collagenous sprue (see below)
- Ulcerative jejunoileitis

Emphasize to the patient the need for **lifetime** gluten restriction.

Now that you know about celiac disease, what test will you remember to order in the following patients?

A 16-year-old presents with a diagnosis of bipolar disorder.

A 33-year-old presents with bone pain in his spine and legs.

A 28-year-old presents with a purulent papulovesicular eruption on her extensor elbows and knees.

A 30-year-old presents with heme-negative stool and low Hgb, MCV, and ferritin.

Good! **Antibody test** for **celiac disease**. Celiac disease is a commonly missed diagnosis.

### Collagenous Sprue

Collagenous sprue is an unusual, possible variant of celiac disease in which the small bowel biopsy shows flattened mucosa with large masses of subepithelial eosinophilic hyaline material in the lamina propria. Collagenous sprue is one cause of failure to respond to GFD treatment.

### Tropical Sprue

Tropical sprue causes malabsorption with partial villous atrophy and is probably caused by an infectious organism. It is endemic in areas of the Caribbean, South Africa, Venezuela, India, and South East Asia (i.e., the **equatorial** areas). Patients often have megaloblastic anemia.

Treatment: tetracycline or TMP/SMX for 3–6 months. Folic acid replacement can also be effective either alone or as adjunctive treatment.

### Whipple Disease

Whipple disease is a seemingly rare disease (< 1,000 cases total; probably under-reported) caused by *Tropheryma whipplei*, a gram-positive actinomycete.

The cardinal tetrad of symptoms:

- 1) Arthralgias—the **most common** symptom preceding diagnosis! (Much more so than abdominal problems!)
- 2) Abdominal pain
- 3) Weight loss
- 4) Diarrhea

Patients may have severe malabsorption—often with marked hypoalbuminemia and neurologic symptoms. Some of these symptoms are the result of lymphatic obstruction.

Upper endoscopy with small intestine biopsy is the diagnostic procedure of choice. Small bowel biopsy shows specific **foamy macrophages** that are positive for PAS staining bacterial remnants. You can also check CSF for *T. whipplei* by PCR, which is **diagnostic** if found.

Treat with **ceftriaxone** or IV **PCN** for 14 days and then treat with TMP/SMX for **1 year**. **Relapse** often manifests with **CNS symptoms**.

DDx: Similar symptoms also may be caused by lymphatic blockage from primary intestinal (or other) lymphoma.

### Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis can mimic **intestinal lymphoma** and **regional enteritis**. Patients have N/V, diarrhea, abdominal pain, weight loss, albumin wasting, and iron deficiency anemia. They often have a **peripheral eosinophilia**; and even though it is thought to be due to an allergy to certain foods—which would be mediated by IgE—only 20% have specific food allergies with an increased IgE.

Treat with corticosteroids short term (2–6 weeks) and avoidance of the causative foods. **Strongyloides** can also cause a peripheral eosinophilia (*Giardia* does **not**), so be sure to rule this out before you start the steroids!

### Short Bowel Syndrome

Short bowel syndrome occurs after massive resection of the small bowel, usually due to:

- severe ischemic injury,
- surgery for small bowel volvulus,
- jejunioileal bypass for morbid obesity, or
- multiple surgeries for Crohn disease.

Short bowel syndrome is likely when there is (roughly) **< 2 feet** (60 cm) of remaining small bowel—especially when the proximal jejunum and/or distal ileum are removed. Lifelong total parenteral nutrition (TPN) is likely to be required if the remaining small bowel is **< 100 cm** and there is loss of the ileocecal valve.

These patients are susceptible to **calcium oxalate** kidney stones (2° steatorrhea) and gastric acid hypersecretion.

Treat short bowel syndrome with a low-fat diet and vitamin supplements. TPN may be needed after large resection and/or while waiting for bowel adaptation after surgery.

### Malabsorption Due to Decreased Digestion

There are 2 main causes:

- 1) **Pancreatic insufficiency**: can be seen in chronic pancreatitis, pancreatic cancer, and cystic fibrosis. Determine pancreatic insufficiency by qualitative stool exam, revealing undigested muscle fibers, neutral fat, split fat, and low levels of fecal elastase.
  - The undigested muscle fibers indicate impaired digestion.
  - Low fecal elastase is characteristic of pancreatic insufficiency steatorrhea.
  - Further confirm impaired digestion by a positive response to treatment with pancreatic enzymes. The d-xylose absorption test may also be done during the workup (discussed below) and is normal.
  - You must rule out pancreatic cancer if there is evidence of pancreatic insufficiency in patients **> 55 years of age**. CT scan frequently shows pancreatic abnormalities.



## Quick Quiz

- What is the clinical presentation of Whipple disease?
- What must be ruled out in a patient older than 55 with pancreatic insufficiency?
- Steatorrhea is the best indicator of \_\_\_\_.
- What is the best screening test for steatorrhea? What is the “gold standard” test?
- What is the significance of a normal D-xylose absorption test in a patient with steatorrhea? Low D-xylose?

### 2) Bile acid deficiency:

- Ileal resection (> 100 cm—see page 1-30) or disease that decreases bile acid uptake
- Severe liver disease, which decreases production of bile acids
- Zollinger-Ellison syndrome (ZES), in which the patient has increased acidity in the small bowel that causes precipitation of bile acids
- Bacterial overgrowth resulting in the breakdown of bile acids, making them useless for fat digestion (discussed below)

**Steatorrhea** is the best indicator of malabsorption because it usually is the most prominent problem:

- The 3-day, quantitative fecal fat measurement is the “gold standard” for determining steatorrhea. Steatorrhea is defined as > 14 g/d of fecal fat.
- Sudan stain of the stool tests for fat and is the best for screening.
- Serum carotene levels are a less specific indicator for malabsorption (see next).

Steatorrhea from **pancreatic insufficiency** causes the **most** fecal fat (can be > 50 g/d). Any patient having > 40 g/d of fecal fat almost certainly has pancreatic insufficiency—barring history of intestinal resection, which can also increase fecal fat to these levels.

### Diagnosing the Cause: Transport vs. Digestion

First, determine whether it is a small bowel **mucosal** problem or a **digestive** problem, by testing directly for celiac disease and chronic pancreatitis. Other common causes of malabsorption are Crohn disease and bacterial overgrowth. A small bowel biopsy may be needed.

The xylose (D-xylose) absorption test is not used much. Still, it is frequently a quiz topic and is still useful for differentiating disorders in carbohydrate absorption.

D-xylose requires normal transmucosal transport; but to be absorbed, it does not require digestion by pancreatic enzymes. Therefore, a **normal** test result in a patient with steatorrhea tells you that mucosal transport is normal. Diffuse small bowel disease can be excluded (i.e., CD, short bowel syndrome) and **pancreatic insufficiency** is **more likely**. These patients are often empirically treated with pancreatic enzymes. Resolution of the symptoms is therapeutic and confirms the diagnosis.

On the other hand, a **low** result can be caused not only by **small bowel disease**, but also by many other conditions, including poor gastric emptying, **bacterial overgrowth**, ascites, renal insufficiency, and old age. But, if the patient definitely has steatorrhea, the diagnosis probably is small bowel disease since most of the other causes of an abnormal xylose test do not cause steatorrhea. So, **xylose test low?** Do a **small bowel biopsy**!

Again, **normal** D-xylose = normal small bowel. Probably **pancreatic insufficiency** as cause of steatorrhea.

The absorption of carotene, vitamin K, vitamin D, folate, and iron also are independent of pancreatic enzyme digestion. So low serum carotene, hypocalcemia, hypoprothrombinemia, and/or Fe deficiency anemia in the patient with steatorrhea suggests a small bowel malabsorption problem rather than a pancreatic disorder. This is true only if steatorrhea is chronic and the patient has a normal dietary intake. Conversely, chronic diarrhea and normal levels of the above indicate pancreatic insufficiency.

An alcoholic who has an elevated prothrombin time easily corrected by vitamin K more likely has malabsorption as the cause of the high PT—not liver disease!

### Summary

When **malabsorption** occurs **with steatorrhea**:

- Low “anything” suggests small bowel mucosal problem or bacterial overgrowth.
- Normal xylose absorption test with normal carotene, calcium, and prothrombin suggests pancreatic insufficiency—especially if there is very high fecal fat.

### Bacterial Overgrowth

There can be combined causes of malabsorption, as in **bacterial** overgrowth, which results in bile acid deconjugation and patchy destruction of intestinal villi.

Patients with bacterial overgrowth usually have moderate **steatorrhea**, but their presenting complaint is often **abdominal distention** and **weight loss**. The overgrowth of bacteria makes more folate but decreases absorption of B<sub>12</sub>, so you can get the odd finding of macrocytosis with **high** folate and low B<sub>12</sub> levels.

Bacterial overgrowth occurs in a variety of conditions:

- Structural abnormalities—diverticula, fistulae, strictures, **after ileocecal resection**.
- Motility disorders—peristalsis is a major mechanism for clearing the small intestine of bacteria. (Peristalsis may be defective in **diabetes** and **scleroderma**.)
- **Achlorhydria**—acid in the stomach kills bacteria before it enters the small bowel.
- **Immune disorders**—immunoglobulins secreted in the small bowel may decrease bacterial growth.

There is data showing a direct causative relationship between bacterial overgrowth and **rosacea**! In this study, almost 50% of patients with rosacea had bacterial overgrowth and 100% of these patients had long-term resolution when their bacterial overgrowth was resolved with a 10-day course of **rifaximin**—a nonabsorbable antibiotic.

Diagnose bacterial overgrowth with the **lactulose hydrogen breath test** (or simply, hydrogen breath test) and sometimes the C14-glycocholate breath test. Also remember the **high folate levels, low B<sub>12</sub>**, and macrocytosis. CT or UGI will show any small bowel diverticula (usually from scleroderma) and dilated small bowel.

The specific overgrowth tests are usually available only at large medical centers. Bacterial overgrowth is often treated empirically with antibiotics after suggestive history and lab findings with:

- **rifaximin** (a nonabsorbable antibiotic that stays in the digestive tract), or
- combination antibiotics (usually amoxicillin-clavulanic acid + metronidazole) that cover anaerobes and aerobes.

### Bowel Resection and Diarrhea

Massive resection of small bowel can cause malabsorption (short bowel syndrome), especially if the **terminal ileum** and ileocecal valve are resected. The ileum absorbs specific nutrients, especially B<sub>12</sub> and bile acids.

> 60 cm of terminal ileum resected: **B<sub>12</sub> malabsorption**.

< 100 cm of terminal ileum resected: Bile acid uptake capacity is decreased, causing bile acid to make it to the colon and cause a bile acid-induced diarrhea.

> 100 cm of terminal ileum resected: Bile acid uptake capacity is lost. Synthesis cannot keep up with loss resulting in bile acid deficiency and subsequent **fat malabsorption**. See under Crohn Disease, Terminal Ileum Problems on [page 1-19](#).

## IRRITABLE BOWEL SYNDROME

### OVERVIEW

A large part of a gastroenterologist's practice consists of **functional** complaints. Around 15% of the population

has signs/symptoms of irritable bowel syndrome (IBS) and **women** are diagnosed with it more often than men (2:1). IBS has characteristic symptoms of frequent, small stools with mucus and abdominal pain relieved by defecation. These symptoms may be either continuous or intermittent. There are no nocturnal or organic symptoms. Patients generally have an increased bowel motor response to **emotional** and **physical** stimuli, but these motor patterns are not specific to IBS. Patients with IBS are more likely to have had psychological or physical trauma in childhood.

## DIAGNOSIS OF IBS

### Overview

Establish diagnosis of IBS by:

- excluding other diseases, and
- looking for characteristic symptoms.

Only infrequently do cases need invasive evaluation with colonoscopy or sigmoidoscopy.

These patients are more likely to have psychosocial dysfunction that doesn't meet criteria for major disorders. They may have neuroses, anxiety, or depression. They are also more likely to have a history of physical or psychological trauma.

Patients > 45 years old with new-onset IBS symptoms warrant a full evaluation.

### Exclude Other Diseases

**Celiac disease:** 2–4% of IBS patients, especially those referred to a secondary center, have celiac disease ([page 1-26](#)), which can be screened out with tissue transglutaminase Ab or antiendomysial Ab tests.

**Lactose intolerance:** Rule out lactose intolerance. Also, consider that 33% of patients with lactose intolerance do not improve on a lactose-restricted diet because they have concurrent IBS!

**Bacterial overgrowth** has been implicated in some cases.

**Sorbitol:** Rule out excessive sorbitol intake from excess ingestion of "sugarless" candies, mints, gums.

### Look for Characteristic Symptoms

The characteristic symptom pattern of abdominal pain and altered bowel habits has been formalized into the International Classification for Irritable Bowel Syndrome—usually called the **Rome criteria**.

The Rome criteria are at least **3 months** of continuous or recurrent:

- Abdominal pain relieved by defecation or accompanied by a change in frequency or consistency of stool, and ...



## Quick Quiz

- What are some important causes of bacterial overgrowth?
- Bacterial overgrowth is associated with what dermatologic condition?
- How do you diagnose bacterial overgrowth as a cause of diarrhea?
- What other diagnoses should be excluded prior to diagnosing a patient with irritable bowel?
- Endocarditis due to \_\_\_\_\_ or \_\_\_\_\_ (organisms) warrants a colonoscopy to search for colon cancer.
- Disturbed defecation at least **25%** of the time, consisting of 2 or more:
  - Altered frequency
  - Altered consistency
  - Passage of mucus
  - Altered stool passage
  - Abdominal distention
 and ...
- **No** constitutional signs or symptoms, such as fever, weight loss, anorexia, and anemia. Specifically, no **nocturnal** symptoms!

## TREATMENT OF IBS

Know the following:

**Reassurance** is paramount, as shown by the very impressive 60–70% (!) response to placebo by these patients—although only 30% have **adequate** relief with placebo. It is critical to form a therapeutic physician-patient relationship.

**Behavioral** and **cognitive** therapies help the psychosocial issues.

**Fiber** supplementation is a traditional standard of care, although more helpful in constipation-predominant IBS.

**Probiotics**, such as *Lactobacillus*, *acidophilus*, and *Bifidobacterium longum* can be tried.

**Antispasmodic** agents used for IBS are anticholinergics (dicyclomine, hyoscyamine): have more side effects than benefits long term. Okay for **short-term** or intermittent use.

**Tricyclic antidepressants** (TCA) in low doses work well for IBS, especially if patients have loose stools, because TCAs slow bowel motility and may improve neuropathic pain.

**Motility drugs:** Loperamide decreases motility, increases sphincter tone, and is good for loose stools.

**Lubiprostone** (Amitiza®) is effective for constipation-predominant IBS.

5-hydroxytryptamine-**3** receptor antagonists have had problems with complications (ischemic colitis and severe constipation). Alosetron was pulled from the market and now is back, but with FDA-boxed warnings. Other agents include ondansetron and granisetron.

5-hydroxytryptamine-**4** receptor agonists have had even more issues (cardiac side effects!), and the only agent in this class—tegaserod—was pulled by the FDA in March 2007. It is now back, under investigational use.

Alternating diarrhea and constipation may be due to patients' use of "stoppers," such as loperamide (e.g., Imodium®), and "starters," such as laxatives.

## COLON CANCER

### OVERVIEW

Colon cancer risk factors:

- Age > 50
- Adenomatous polyps (current or past)
- Ulcerative colitis
- Crohn colitis
- *BRCA1* mutation
- Acromegaly
- Obesity
- Smoking

Hereditary and environmental **risk** factors:

- 1<sup>st</sup> degree relatives with colon cancer or adenomatous polyps
- Familial polyposis (FP) syndromes (see next)
- Diets high in calories and animal fat
- Hereditary, nonpolyposis colon cancer (HNPCC—see below)

Lifetime risk of colon cancer is 4% in average-risk persons.

Diagnostic flags for colon cancer:

- Anorexia
- Weight loss
- Anemia
- Fever
- Heme+ stools
- Change in bowel habits, especially with nocturnal stools
- Onset of symptoms after age 45

Remember: Endocarditis caused by either *Streptococcus bovis* or *Clostridium septicum* is often associated with **colon cancer**, so conduct a thorough GI workup in these patients.

Low-dose aspirin (81 mg) appears to cause a mild reduction in the risk of development of recurrent colon adenomas, but low-dose aspirin alone is not enough to decrease colon cancer risk. Full-dose aspirin is necessary for reducing risk of colon cancer. Protective effect of aspirin is related to:

- Dose of aspirin
- Frequency of use per week
- Duration of use (years)

Most GI cancers arise from **adenomas**. (Image 1-17, Image 1-18). 25% of colorectal cancers are located beyond the splenic flexure.

Adenomas with “**advanced**” features are defined as any of the following:

- Presence of high-grade dysplasia
- Presence of villous histology
- Size > 10 mm

“**Advanced**” means likely to develop into cancer. Progression to cancer from an early adenoma takes 5–10 years. Diet plays a role in GI cancer—**possible** dietary factors include high animal protein and fats, low fiber, and low calcium. Be sure and discuss these important considerations with patients on a “low-carb” diet!

Again, **large** or **villous** adenomatous polyps are **likely** to harbor or progress to **cancer** (Table 1-5).

Perspective: ~ 30% of people > 40 years old have adenomatous polyps, but only 1% of adenomatous polyps ever become malignant.

**Hyperplastic** polyps have **no** malignant potential and contain **no** features of dysplasia. This makes sense because hyperplasia, by definition, is **increased growth** of **normal** tissue.

After polyps are found, follow-up depends on the type of polyp, size, number found, and family history. Only **adenomatous** polyps require specific follow-up. Hyperplastic polyps, if < 1 cm (except for those with a hyperplastic polyposis syndrome), have the same follow-up as no polyp (10 years).

The 2008 American Cancer Society (ACS) guidelines recommend the following:

- Patients with **1** or **2** small tubular **adenomas** with low-grade dysplasia should have repeat colonoscopy **5–10** years after initial polypectomy.

Table 1-5: Malignant Potential vs. Size

|            | < 1 cm | 1–2 cm | > 2 cm |
|------------|--------|--------|--------|
| Tubular    | 1%     | 10%    | 34%    |
| Mixed (TV) | 4%     | 9%     | 45%    |
| Villous    | 10%    | 20%    | 54%    |

- Patients with **3–10 adenomas**, or 1 adenoma > 1 cm, or any adenoma with **villous** features or **high-grade** dysplasia should have repeat colonoscopy in **3** years.
- Patients with **> 10 adenomas** should have repeat colonoscopy **< 3 years**. (Consider the possibility of an underlying familial syndrome—see below.)
- Patients with **sessile** adenomas that are removed piecemeal require repeat colonoscopy in **2–6 months** to verify complete removal.

## INHERITED COLON CANCER

### Overview

Inherited colon cancer can be categorized into either polyposis or non-polyposis syndromes.

### Familial Polyposis Syndromes

The familial (or hereditary) polyposis syndromes are all **autosomal dominant** (AD).

Four types, in order of **decreasing** cancer potential. The first 2 are adenomatous, the second 2 are hamartomatous:

- 1) **Familial adenomatous polyposis (FAP)**—hundreds of **adenomas** in the **colon**—100% risk of cancer if not treated. **These patients require a proctocolectomy by age 20!** They can also get some duodenal adenomas, which also have a high risk of cancer. After colectomy, patients with FAP tend to get duodenal cancer next. They are also at increased risk of developing secondary tumors (ampullary adenomas, cancers). Giant stomach tumors are common in FAP patients, but they are **benign**.
- 2) **Gardner syndrome**—a variant of FAP with more extraintestinal benign growths. The adenomas have the same risk of cancer as FAP (100%). These patients often have bone lesions (**osteomas**) and soft tissue tumors. Treatment is the same as FAP. Question: Patient has multiple osteomas found incidentally on an x-ray. What do you do? Colonoscopy!
- 3) **Peutz-Jeghers syndrome**—multiple hamartomatous polyps throughout the small bowel, and occasionally in the colorectum and stomach, plus melanotic pigmentation (freckles) on the lips and buccal mucosa. The most common presentation is with abdominal pain due to intussusception or bowel obstruction by

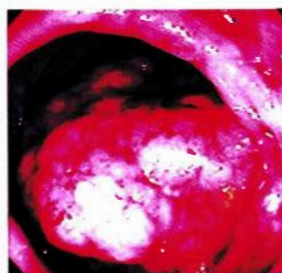


Image 1-17: Colon cancer

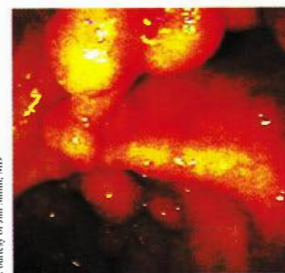


Image 1-18: Polyps in the colon



## Quick Quiz

- What size and histology findings of colon adenomas are considered “advanced features” with increased malignant potential?
- What is the relationship between hyperplastic polyps and colon cancer?
- Know the 2008 ACS guidelines for recommendations on follow-up intervals based on type and number of polyps.
- Which 2 familial polyposis syndromes have the highest risk of carcinoma? Which has **no** risk of carcinoma?
- What is the risk of cancer in a patient with Peutz-Jeghers?
- At what age does screening begin for HNPCC?
- Under what circumstances should periodic colonoscopy be started at age 40?

a large polyp. Even though these polyps are **hamartomas**, which have no risk of cancer, there is still some risk of cancer because there are occasional adenomas that can become carcinomas. Risk of cancer is 50% by 60 years of age.

- 4) **Juvenile polyposis** also consists of hamartomas. This is the **only** one of these syndromes with **no** malignant potential. No follow-up needed.

### Hereditary Nonpolyposis Colon Cancer

Most patients with this form of cancer do **not** have a familial polyposis; rather, the cancer arises from normal-appearing epithelium.

Hereditary nonpolyposis colon cancer (HNPCC, or Lynch syndrome) can be defined as “the occurrence of colon cancer in at least **three 1<sup>st</sup> degree** relatives over at least **2** generations, and with at least **1** person diagnosed < age 50.” These rather loose diagnostic criteria place Lynch syndrome in as many as 1 in 20 (5%) patients with colon cancer! Women in families with HNPCC have an increased incidence of **ovarian** and **endometrial** cancer as well as renal, ureteral, stomach, pancreatic, and biliary tree cancers.

Start screening those with HNPCC risk profile at age **25**.

## SCREENING

### Review

Current screening recommendations are also covered in the General Internal Medicine section, Book 5, under Screening Tests. In general, do yearly multiple card fecal occult blood testing (FOBT) in low-risk patients.

The 2008 American Cancer Society guidelines for colorectal cancer screening for asymptomatic adults  $\geq 50$  years of age with a negative family history for colon cancer or adenomatous polyps have broken down the tests into the following 2 areas:

- 1) Tests that detect adenomatous **polyps** and **cancer** (preferred by the guideline-writing committee):
  - Colonoscopy every 10 years, or
  - Flexible sigmoidoscopy every 5 years, or
  - Double-contrast barium enema every 5 years, or
  - CT colonography every 5 years
- 2) Tests that primarily detect **cancer**:
  - Annual fecal **immunochemical** test with high sensitivity for cancer, or
  - Annual **guaiac**-based fecal occult blood test with high sensitivity for cancer, or
  - Stool **DNA** test with high sensitivity for cancer, interval uncertain

Each strategy has inherent strengths and weaknesses. FOBT is the most inexpensive and obviously least invasive, but it may miss  $\sim 1/3$  of advanced cancers. Colonoscopy has the **highest yield** of finding polyps and cancers, but is most costly and invasive. Guidelines recommend that any positive test (other than colonoscopy) should be followed up by a full colonoscopy with biopsy of any identified abnormalities/polyps. The 2008 USPSTF guidelines generally agree with the American Cancer Society Guidelines except that the USPSTF recommends **against** screening in those  $> 85$  years of age.

Repeat colonoscopy every 3 years thereafter if polyp is benign.

### The “10 year” rule.

Increased-risk patients: Surveillance (colonoscopy) should be at age 40 years or 10 years before age at which index case is diagnosed—whichever is first.

For example: Start at age 40 if a 1<sup>st</sup> degree relative was diagnosed with an adenoma or colon cancer at age 52; start at age 20 if several 1<sup>st</sup> degree relatives had colon cancer at age 30.

**Colonoscopy** is the screening procedure of choice if **any 1<sup>st</sup> degree** relatives have had colon cancer or an adenomatous polyp, **or** if an adenomatous polyp has ever been found in the patient. Time between surveillance colonoscopies is dependent on the cancer potential of the polyp: See previous discussion, under Colon Cancer Overview.

Virtual colonoscopy or CT colonography is a CT scan with special software in a totally prepped patient. It has high yield for detecting **larger** polyps and cancers. Areas of adherent stool can be mistaken for small polyps. However, it is an excellent test for a patient who cannot complete a standard colonoscopy to visualize the entirety of the colon. If abnormalities are found on CT colonography, the guidelines recommend, if possible, going

**Table 1-6: Indications for Colonoscopy**

Occult bleeding

**Fe deficiency anemia unless other explanation**

Gross lower GI bleeding except bright red blood in a younger person

**Abnormal barium enema**

Adenomatous polyp—initially and for all follow-ups

**History of colon cancer**1<sup>st</sup> degree relative of one with colon cancer**Familial polyposis syndromes, HNPCC/Lynch syndrome**

IBD: Suspicion, follow-up, surveillance

***Strep bovis*, *Clostridium septicum* bacteremia**

Ischemic colitis

**Persistent diarrhea with negative blood tests and not meeting criteria for diagnosis of IBS**

4–8 weeks after new-onset, presumed diverticulitis to rule out colon cancer

straight to colonoscopy since the patient has already been prepped; otherwise, the patient will have to return and do another bowel prep.

Sigmoid colon cancer can perforate the bowel wall and simulate diverticulitis. So, screen for colon cancer after **diverticulitis** in **older** patients. See **Table 1-6** for the most frequent indications for colonoscopy.

## FOBT

Fecal occult blood testing (FOBT) is positive in about 2%. This varies with age; > 5% after 60 years of age. Of positive FOBTs, 2% have GI cancer.

Remember: The FOBT is negative in up to 66% of patients with colon cancer. Using 6 Hemoccult<sup>®</sup> cards (the full FOBT series) will detect advanced colonic cancer in only about 25% of patients. This makes it a pretty poor screening test, but it is used (annually or biennially) because it is quick and cheap.

Even if **one** FOBT is positive, do a **colonoscopy**. A flex-sig + ACBE (air-contrast barium enema) is also acceptable but clearly less desirable.

## CEA

Note: Carcinoembryonic antigen (CEA) levels are good **only** in checking for **recurrence** of colon cancer—and only if levels were **elevated before** surgery and **reduced after** surgery. CEA may also be mildly elevated in patients who smoke or who have benign biliary disease, sclerosing cholangitis, or IBD.

## STAGING OF COLON CANCER

### TNM Classification

The 2 methods for staging colon cancer are TNM and Duke's. They are similar, but TNM is the preferred classification method and was updated in 2010.

In general, the cancer stage becomes more advanced as the tumor enlarges and invades the colonic wall:

- TNM stage I: extends into submucosa (T1) or muscularis (T2); no nodal involvement; no metastases
- TNM stage II (subclassifications A, B, C): extends past muscularis into tissues around the colorectal area (T3) or into visceral peritoneum (T4a) or is directly invasive (T4b); no nodal involvement; no metastases
- TNM stage III (subclassifications A, B, and C): any combination of T1–T4b with nodal involvement and no metastases
- TNM stage IV: any combination of T1–T4b, any N, with distant metastases

Colon cancer virtually always metastasizes to the liver first (via portal circulation). However, if it involves only the **rectum**, the blood supply bypasses the portal circulation, so the patient may have lung, bone, and brain mets **without** liver mets.

## TREATMENT OF COLON CANCER

**Surgical resection** is the 1<sup>st</sup> treatment option and is potentially curative. Recurrences after surgery are probably due to micrometastases.

Adjuvant chemotherapy consists of a 5FU-based therapy. Typically, 5FU plus leucovorin (LV) is used. Recently, trials have shown benefit from oxaliplatin being added to this regimen. This protocol is called **FOLFOX**.

Adjuvant chemo is effective only for stage III or locally advanced II.

Radiation therapy prior to surgery is helpful for **rectal** lesions only.

Hepatic resection increases survival with **solitary** liver mets.

If you remove a cancerous polyp, you must do a bowel resection if the cancer extends to either a blood vessel or the cautery line.

## DIVERTICULAR DISEASE AND LOWER GI BLEED

### DIVERTICULAR DISEASE

#### Types of Diverticular Disease

There are 4 types of diverticular disease (see **Image 1-19** and **Image 1-20**):

- 1) **Asymptomatic** diverticulosis (most common)
- 2) Painful **diverticulosis** (contraction of hypertrophied colonic muscle)



## Quick Quiz

- What common colon problem in older patients is an indication for colonoscopy?
- Are CEA levels useful for primary diagnosis, recurrence, or both in colon carcinoma? Why?
- Surgery for cure is the rule in colon cancer. When is adjuvant chemotherapy used? When is radiation used?
- What may be seen on abdominal CT scan in a patient with diverticulitis?

3) Diverticular **bleeding**

4) **Diverticulitis**

### Asymptomatic Diverticulosis

Diverticulosis is the presence of one or more diverticula in the colon. Incidence increases with age. About **80–85%** never have symptoms. It has been assumed that diverticulosis is caused by a low-fiber diet and can be warded off by a high-fiber diet. A recent study (2011) casts doubt on the theory of a low-fiber diet being the cause of diverticulosis. Current guidelines still recommend high-fiber diet for those with asymptomatic and symptomatic diverticulosis.

### Symptomatic Diverticulosis

**Painful** diverticulosis is due to hypertrophy of both circular and longitudinal colonic musculature, which leads to luminal narrowing, pencil-thin stools, and bouts of colicky pain often relieved by passing flatus or having a bowel movement. This occurs in about **10–15%** of diverticulosis patients.

Treat with **bulking agents** which typically contain psyllium or methylcellulose.

### Diverticular Bleeding

Diverticular bleeding occurs in only a few of those with diverticulosis. Even so, diverticular bleeding is the **most common** cause of colonic bleeding in the elderly;

**angiodysplasia** is next on the list and often results in more severe bleeds. Diverticular bleeding usually originates in the sigmoid colon, and typically stops spontaneously. Patients classically present with “**painless, maroon stool**,” but it can vary from black to red.

Treatment for diverticular bleeding: Stabilize patient if needed, rule out UGI bleed with NG aspirate or endoscopy. Colonoscopy only if bleeding doesn't stop. Note: UGI bleed is suggested by a **BUN/Cr ratio** > 30:1, which indicates blood is being digested and breakdown products are being absorbed.

Diagnose diverticular bleeding with colonoscopy or technetium-tagged RBC scan. Angiography works if bleeding is severe or continuous.

See **Table 1-7** for common indications for GI angiography.

### Diverticulitis

Diverticulitis is caused by inflamed diverticula. It is usually due to **microperforations**. It occurs in **< 5%** of diverticulosis patients. Signs and symptoms include:

- LLQ pain
- Fever
- High WBC
- LLQ tenderness
- No bleeding!

The LLQ tenderness is usually localized and may have rebound tenderness. Look for a **sigmoid mass** (i.e., palpable, tender sigmoid) on physical exam, on U/S, or on CT. CT is most useful in assessing diverticulitis: It may show areas of **thickened sigmoid colon** or **pericolic fluid** accumulation. **Avoid colonoscopy** on any patient with diverticulitis (due to risk of perforation).

Treatment of diverticulitis should cover both **aerobic** and **anaerobic gram-negative** organisms.

Treat **mild** diverticulitis in a patient able to drink and without peritoneal signs with outpatient **metronidazole** (gram-neg anaerobic) plus either **ciprofloxacin** or **TMP/SMX** (gram-neg aerobic) and close follow-up.

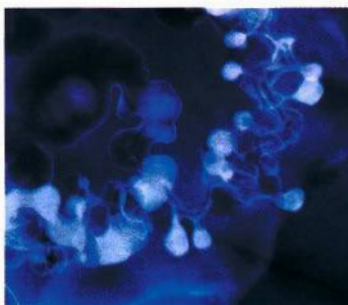


Image 1-19: Intestinal diverticulosis, x-ray



Image 1-20: Diverticular disease

Table 1-7: Angiography in GI Disease

Chronic and acute mesenteric ischemia

Severe lower GI bleed

Rarely used for UGI bleed—some duodenal ulcers

TIPS in variceal bleeding

Therapeutic uses: embolization, vasopressin

Treatment of moderate-to-severe diverticulitis:

Inpatient parenteral treatment for those with peritoneal signs may consist of one of the following:

1) **Dual-drug therapy (best!)**, such as:

- aminoglycoside or ciprofloxacin (gram-negative aerobic)

**plus**

- clindamycin or metronidazole (gram-negative **anaerobic**)

**or**

2) **Single-drug therapy**, such as:

- Ticarcillin/clavulanic acid
- Piperacillin/tazobactam
- Imipenem/cilastatin
- Ampicillin/sulbactam
- Cefotetan

All these single-drug therapies cover **both** aerobic and **anaerobic** gram-neg organisms.

Drain abscesses percutaneously.

Perforation from sigmoid **colon cancer** can present similarly to diverticulitis, so follow up patients > 50 with a flex-sig/colonoscopy 4–8 weeks after the acute condition resolves.

Meckel diverticulum is the most frequent congenital GI anomaly. Although < 1/2 of these diverticula have **gastric mucosa**, only these ulcerate and bleed. Meckel diverticula cause 1/2 of all GI bleeds in children; they can also cause obstruction and intussusception. They may be seen with the technetium scan ("Meckel's scan"). Technetium is taken up by **gastric mucosa**.

## ANGIODYSPLASIA AND LOWER GI BLEED

Angiodysplasia (= vascular ectasia, = AVM) is the 2<sup>nd</sup> most common cause of lower GI bleeding in the elderly (diverticular bleeding is 1<sup>st</sup>). Think of these as spider nevi of the GI tract.

Bleeding in angiodysplasia may be occult to severe. The usual bleeding site is the right colon (cecum, ascending).

AVMs typically are not cauterized unless they are bleeding significantly.

Hereditary hemorrhagic telangiectasias (HHT, = Osler-Weber-Rendu) is the hereditary condition in which there are multiple AVMs affecting all the organs, including brain, lung, skin, and mucous membranes and the GI tract—especially in the **upper** GI tract (AVM is usually lower). Patients with HHT often have a history of **epistaxis**.

Angiography may be used in workup of severe disease (again, see [Table 1-7](#)).

Endoscopic treatment can help, although there are often many lesions and not all can be treated.

## COLONIC ISCHEMIA (Ischemic Colitis)

Colonic ischemia (CI; ischemic colitis) causes **abdominal pain** (from the ischemia) and **maroon** stools. See more below.

## VIDEO CAPSULE ENDOSCOPY

Okay, with EGD you can see the upper GI tract, and there is colonoscopy for the lower GI tract. The wireless video capsule endoscopy (VCE) is used to visualize the previously unvisualizable small bowel. It is especially useful in working up small bowel bleeds or occult blood loss without an obvious cause.

Know! The **typical scenario** is a patient presenting with a history of episodic melanotic stools with negative EGDs and colonoscopies.

The VCE is also becoming useful for other small bowel problems; e.g., assessing tumors, Crohn disease, and celiac disease.

## BOWEL OBSTRUCTION

The most frequent cause of **small intestine** obstruction is postoperative **adhesions**. In decreasing order, the most common causes of **colonic** obstruction are: **carcinoma**, then **diverticulitis**, then **volvulus**.

The diagnosis of obstruction is made with a flat and upright abdominal film showing (typically) excessive amounts of air in the small bowel with no air in the colon. The presence of air fluid levels is helpful when there are "J-loops," in which the air fluid levels are at different heights on either side of the same loop of bowel. This signifies a dynamic obstruction. If the fluid levels are the same height on either side of the loop, **paralytic ileus** is the more likely diagnosis.

Treat with IV fluids and NG suction. Further workup is indicated if the symptoms do not resolve in 1–2 days. Gastrografin enema can be helpful if the obstruction is thought to be of colonic origin.

## INTESTINAL ISCHEMIA

### TYPES

There are 4 types of intestinal ischemia:

- 1) Colonic ischemia (most common)
- 2) Chronic mesenteric ischemia
- 3) Acute mesenteric ischemia (70% mortality!)
- 4) Mesenteric venous thrombosis

## COLONIC ISCHEMIA (Ischemic Colitis)

Colonic ischemia (CI; ischemic colitis) is the most common form of intestinal ischemia. It is due to a **non-occlusive** ischemia—mostly involving some portions of



## Quick Quiz

- What is the treatment of moderate-to-severe diverticulitis?
- What is “thumbprinting,” and when is it seen?
- What is the clinical presentation of chronic mesenteric ischemia?
- What is the clinical presentation of acute mesenteric ischemia?

the splenic flexure, descending colon, and/or sigmoid colon; i.e., inferior mesenteric circulation. Most often, **no specific cause** for the ischemia is found. It is a disease of the elderly and may be seen post-op (colonic surgery and aortic aneurysmectomy); it is occasionally associated with **low-flow conditions** (CHF) and **hypercoagulable** states. Because this condition is virtually **never embolic**, patients are **not** likely to have valvular heart disease or cardiac arrhythmia.

Symptoms of CI: usually a sudden LLQ pain with an urge to defecate, followed by passage of red-to-maroon stool within 1 day.

Mildest injury: mucosal and submucosal hemorrhage and edema—which is completely reversible. More severe injury ranges from replacement of mucosa and submucosa with granulation tissue to transmural infarction and fulminant colitis.

Submucosal hemorrhage and edema are seen on abdominal x-ray (KUB) or barium enema (BE) as “thumbprinting.” This thumbprinting lasts only a few days and is not specific for the type of ischemia, just for submucosal edema or hemorrhage. CT scan is usually the 1<sup>st</sup> diagnostic test.

If there are no signs of peritonitis, diagnose with **colonoscopy** (which is usually done **without** bowel prep to reduce risk of decreasing blood flow due to use of dehydrating agents). Also okay is sigmoidoscopy. Angiography is **not** usually done.

The usual treatment for colonic ischemia is bowel rest, fluids, and antibiotics. Most will resolve. In rare cases, stricture or acute abdomen develops.

## CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia is also called **intestinal angina**. Patients may have the classic triad:

- 1) Abdominal pain after meals
- 2) Abdominal **bruit**
- 3) **Weight loss** (from tolerating only smaller meals)

The pain is due to episodes of inadequate blood flow brought on by digestion.

Suspect mesenteric vascular ischemia in the above setting, especially if **abdominal pain is out of proportion** to any physical findings.

Symptoms are **1–3 hours of dull, gnawing** abdominal pain beginning shortly after eating. The etiology is atherosclerosis of the intestinal arteries, with the symptoms caused by gastric “steal” after eating. Patients often have signs of other types of peripheral vascular disease (PVD) and often have a smoking history.

Diagnosis is mainly based on **symptoms**. The next step is usually an **MRA** (magnetic resonance angiogram) or CT angiogram, with good sensitivity for proximal lesions, such as superior mesenteric or celiac arteries, but much less sensitive as the involved lesion becomes more distal. Splanchnic angiography is then done if these are abnormal.

Treatment is surgical bypass or angioplasty.

## ACUTE MESENTERIC ISCHEMIA

Acute mesenteric ischemia (AMI) is the most severe form of intestinal ischemia, with an average mortality rate of 70%—even with treatment! It results from acute loss of blood flow to part or all of the small intestine and/or ascending colon.

AMI is seen in older patients with a history of CHF, recent MI, cardiac arrhythmias, or hypotensive episodes.

Patients often have symptoms of intestinal angina (above) for months before the event. Because this condition is **commonly** due to **emboli**, patients **are** likely to have valvular heart disease or cardiac arrhythmia. These patients are **acutely ill** with vomiting, diarrhea, and occult blood.

Bowel infarction leads to acidosis, increased lactate, and elevated amylase. Abdominal pain is disproportionate to the abdominal exam that may be fairly benign, leading to the erroneous diagnosis of acute gastroenteritis.

Do **angiography** unless there are signs of **perforation** (e.g., acidosis, high amylase)—in which case the patient goes directly to surgery for dead-bowel resection and possible embolectomy.

## MESENTERIC VENOUS THROMBOSIS

Mesenteric **venous** thrombosis (MVT) is associated with hypercoagulable states, such as deficiencies of antithrombin III, prothrombin 20210A (a gene variant), protein S, protein C, and *Factor V Leiden* defect.

MVT is also linked to any of the following:

- Pancreatitis
- Liver disease (cirrhosis)
- Intraabdominal sepsis
- Sickle cell disease
- Paroxysmal nocturnal hemoglobinuria (PNH)

MVT may be **acute**, **subacute**, or **chronic**. Like mesenteric infarction, the pain of MVT is often out of proportion to the abdominal exam. If the portal or splenic veins are

involved in **chronic** MVT, there may be bleeding from **gastroesophageal varices**. Cirrhosis patients with coagulopathy can still develop MVT.

**CT** is the diagnostic procedure of choice—on CT, > 90% of MVT can be diagnosed.

Treat **acute** MVT with **thrombolytics** and **long-term anti-coagulants**. Treatment of **chronic** MVT is focused on minimizing bleeding from varices with sclerotherapy, portosystemic shunts, or similar devices.

## CONSTIPATION

### CAUSES

Causes of chronic constipation are many, but they usually result in:

- generalized or regional colonic inertia, and
- pelvic floor muscle dysfunction.

The large majority (> 90%) of cases are **idiopathic**! Lifestyle habits, such as a change to low-fiber diet; sudden, prolonged inactivity; and high stress may result in constipation.

**Recent onset** of constipation without change in lifestyle habits (e.g., **no changes to diet, no new medications**) suggests an **obstructing** lesion (neoplasm, stricture, foreign body). Pelvic floor dysfunction acts like outlet obstruction. Hysterectomy leads to refractory constipation in 5% of patients.

Neurologic causes affecting the parasympathetic innervation of the distal colon and rectum cause **acquired megacolon**; e.g., traumatic sacral nerve damage, MS, Chagas disease, or aganglionic megacolon (Hirschsprung's). **Chagas disease** is found in Central and South America. It is caused by infection with *Trypanosoma cruzi*, resulting in **achalasia**, cardiomyopathy, and acquired megacolon. Aganglionic megacolon (Hirschsprung's) is usually diagnosed within the first 6 months of life, but a milder variant may present in adult patients.

Drugs with **anticholinergic** properties are common causes of constipation. These include antipsychotics, antidepressants, 1<sup>st</sup> generation antihistamines, anticholinergic cold medications, and **especially narcotics**. Other causes include iron preparations, calcium supplements, calcium channel blockers, and antacids containing aluminum or calcium.

Endocrine disorders, such as **diabetes mellitus** (DM) and **hypothyroidism**, often cause mild constipation. Myxedema may result in acquired megacolon. The altered progesterone and estrogen levels are the probable cause of constipation in **pregnancy**.

Collagen vascular diseases, especially progressive systemic sclerosis, also cause constipation.

Many of these causes of constipation can be determined with a careful history.

### DIAGNOSIS

Whom do you work up for constipation? Patients with constipation who additionally have **weight loss, rectal bleeding, or anemia** should get:

- A colonoscopy (to exclude structural disease; e.g., cancer, strictures)
- Serum Ca<sup>++</sup> and TSH (to exclude hyper/hypocalcemia and hypothyroidism; DM is usually evident from the history)

For intractable constipation, test for colonic transit function. 24 radio-opaque markers ("Sitz markers") are taken by capsule, and a flat plate of the abdomen is done 5 days later. Normally, most markers are gone. It is abnormal for  $\geq 5$  to be retained. If the markers are spread **throughout** the colon, the cause is **generalized colonic inertia**. **Clustering** of markers in the **rectosigmoid** colon indicates pelvic floor dysfunction.

### TREATMENT

Treatment of constipation consists of correcting any reversible cause. If idiopathic or irreversible, treatment is increasing dietary fiber to 25–30 g/day and assuring fluid intake > 2.0 liters/day.

Note: Fiber or bulking agents often help with colonic inertia but **not** with pelvic floor dysfunction, which often responds to pelvic floor retraining (+/- biofeedback).

Increase exercise.

Short-term use of an osmotic laxative and/or stool softener is okay. Avoid stimulant laxatives.

Difficult cases usually respond well to daily use of polyethylene glycol powder with water or the recently approved lubiprostone (Amitiza®). Surgical treatment is indicated only for Hirschsprung disease.

Osmotic laxatives (polyethylene glycol, sorbitol, glycerine, etc.) cause increased fluid movement into the lumen, increasing fecal bulk.

Stimulant laxatives (senna or bisacodyl) cause colonic muscles to contract. They are indicated only for short-term use.

Prophylaxis: When you initiate narcotic treatment, also start a stool softener + fiber supplement "bowel regimen" to reduce the risk of iatrogenic constipation.

### FECAL IMPACTION

Fecal impaction is a large mass of dry, hard stool in the rectum causing constipation. Those at greatest risk are elderly persons with inadequate fluid intake who are also on narcotics or anticholinergics, or who have decreased mobility.

Often, more proximal watery stool will leak around the impaction causing a watery fecal incontinence.



## Quick Quiz

- Most cases of constipation are due to what?
- What common gynecologic surgery leads to constipation in 5% of patients?
- What is the clinical presentation of fecal impaction?
- What are the most common causes of pancreatitis in the U.S.?
- What happens to serum amylase and lipase levels over time with acute pancreatitis?
- What 2 relationships do high triglyceride levels have with acute pancreatitis?
- What physical findings reflect severe pancreatic necrosis with multiple organ failure?
- What is Cullen sign? What is Turner sign?

Presentation is sudden onset of watery stools/incontinence in a person with chronic constipation.

Treatment is to **remove** the impaction. Initially, you can try a mineral oil enema, but often the impaction must be manually removed by breaking off small pieces until the obstruction is cleared. Longer-term treatment focuses on remedying the constipation: docusate stool softeners and bulk-forming agents used along with a bowel-training program (daily/regular BMs).

## PANCREAS

### ACUTE PANCREATITIS

#### Overview

Acute pancreatitis is usually caused by either **alcohol abuse** or **gallstones**; these are the #1 and #2 etiologies in the U.S. In Europe, the reverse appears to be true. These are not firm conclusions; results from studies are influenced by where they are done. For example, if the study is done in a VA hospital, the primary cause will probably be alcohol abuse, whereas, if it is done in a community hospital, gallstones are more likely to cause the majority of cases.

Endoscopic retrograde cholangiopancreatography (ERCP) causes acute pancreatitis (see [page 1-1](#)) in 5–20% of patients.

Other causes of acute pancreatitis are acidosis (as in DKA), hypertriglyceridemia, hypercalcemia, trauma, and other problems that result in obstruction of the ampulla of Vater (e.g., pancreatic cancer).

Quite a few drugs can cause acute pancreatitis:

- Diuretics: furosemide and thiazides
- Estrogens

- Azathioprine
- 5-ASA derivatives
- Antibiotics: tetracycline and sulfonamides
- Anti-HIV drugs; e.g., pentamidine and ddI
- Oral hypoglycemics
- 6-mercaptopurine, L-asparaginase, and valproic acid

Many initially “idiopathic” cases of pancreatitis are due to biliary microlithiasis, cystic fibrosis, hereditary pancreatitis, or hypertriglyceridemia. Always check medications.

With acute pancreatitis, amylase and lipase are usually elevated. The serum amylase level is almost always elevated early on ( $> 3\times N$  is almost always due to pancreatitis) but decreases within 2–3 days after disease onset. The lipase level increases later and stays elevated longer than the amylase (beyond day 7).

High triglyceride levels in the setting of acute pancreatitis may cause a spuriously **normal** amylase level!

Additionally, triglyceride levels  $> 1,000 \text{ mg/dL}$  can cause pancreatitis.

### Severity of Pancreatitis

#### Factors and Results

The severity of acute pancreatitis is directly related to the degree of pancreatic **necrosis** (10% have necrosis) and whether this necrotic tissue is **infected** (mortality = 30%) or not (mortality = 10%). Overall, mortality rate for acute pancreatitis = 5–10%!

Severe pancreatitis causes **multiple organ failure**, which is reflected by:

- Hemoconcentration
- Heart: systolic BP  $< 90 \text{ mmHg}$ ; tachycardia  $> 130 \text{ bpm}$
- Lungs:  $\text{PO}_2 < 60 \text{ mmHg}$
- Renal: progressive azotemia **or** oliguria to  $< 50 \text{ mL/hr}$
- CNS: altered sensorium
- Metabolic: low **calcium** ( $< 8 \text{ mg/dL}$ ) and **albumin** ( $< 3.2 \text{ g/dL}$ )

These multiorgan failure indicators are used in several methods of assessment for severity.

### Assessing Severity

#### Skin Signs

Okay, so we know severity of pancreatitis is associated with the degree of necrosis and signs of multiple organ failure. How do we determine severity on admission?

Good clues are the skin signs that may be seen with severe acute pancreatitis:

- The most **common** skin finding is an **erythema** of the flanks caused by extravasated pancreatic exudates.
- Cullen sign and Turner sign, when seen (unusual), indicate a **severe** necrotizing pancreatitis:
  - Cullen sign, a faint blue discoloration around the umbilicus, indicates **hemoperitoneum**.

- Turner (or Grey-Turner) sign, a bluish-reddish-purple or greenish-brown discoloration of the flanks, results from tissue catabolism of hemoglobin from retroperitoneal blood dissecting along the tissue planes.
- Cullen and Turner signs are characteristic but **not** pathognomonic of acute pancreatitis. Cullen sign is also seen with intraperitoneal bleeding (especially ruptured ectopic pregnancy), and Turner sign is seen with other causes of retroperitoneal bleeding.

### Severity Scoring Systems

Multiple systems have been developed over the years, including Ranson and Glasgow. However, neither of these has been shown in large studies to have sufficient sensitivity or specificity.

Newer systems are the Apache II and the BISAP score:

**APACHE II** has been shown to have good sensitivity and specificity, although adding body mass index (APACHE 0) has produced conflicting results. In addition, APACHE II scoring requires **calculators** to perform.

**BISAP** (BUN > 25, impaired mental status, SIRS, age > 60 years, pleural effusion) has similar reliability for mortality (but not other indices) to the APACHE II—with the added benefit that BISAP can be done at the bedside.

**SIRS** (systemic inflammatory response syndrome score) has been validated in smaller studies, is also easily done at the bedside, and can be repeated daily. It is typically used for inpatient daily follow-up assessment.

SIRS is a measurement of the body's physiologic response to an undefined insult (infectious or not) and does not necessarily require multiple organ failure. SIRS is part of a somewhat newer method of categorizing severe illnesses. For instance, sepsis is defined as SIRS plus a documented or presumed infection.

SIRS requires 2 or more of the following:

- Temperature < 36° C (96.8° F) **or** > 38° C (100.4° F)
- Tachycardia (HR > 90)
- Tachypnea (RR > 20 **or** pCO<sub>2</sub> < 32)
- WBC abnormal (> 12 K **or** < 4 K **or** > 10% bands)

### Current AGA Recommendations

Currently, the AGA recommends the following to assess severity:

- Use the APACHE II score **≥ 8** as a cutoff for severe disease.
- Clinical judgment is still important.

Independent risk factors include:

- Morbid obesity (**BMI > 30**) is associated with a 2.1x increase in mortality.

- Hemoconcentration (> **44%**)—but studies are inconsistent regarding the significance of this finding.
- Age > **75**.
- Organ failure.

Pancreatic necrosis is best confirmed by dynamic **CT scan** or MRI (at some centers). It is considered severe if **≥ 30%** of the pancreas is necrotic.

When following after admission, do a SIRS evaluation daily and look for signs of multiple organ failure. Worsening indicators equal worsening severity. ICUs may also use the APACHE system.

### Fluid / Masses in Acute Pancreatitis

Types of fluid collections and masses found in acute pancreatitis:

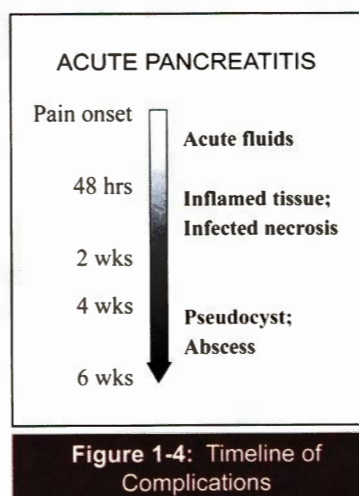
**Acute fluid collections** with high amylase levels appear in up to 50% of patients within **48 hours** of **pain** onset. They usually resolve spontaneously. A sympathetic transudative left pleural effusion frequently occurs. Rarely, a diaphragmatic defect into the pleural space causes an effusion high in **amylase** (**Figure 1-4**).

**Necrotic tissue:** Inflamed, edematous, necrotic pancreas occurs in the first 1–2 weeks and may simulate a pseudocyst (which usually occurs later; discussed below). It can be differentiated from a pseudocyst by ultrasonography. This condition is **serious** and may require drainage.

**Infected necrosis:** **Infected** pancreatic **necrosis** usually requires either drainage (endoscopic or CT-guided) or surgery (infrequent now) **within 2 weeks** of the episode. You can diagnose by CT-guided aspiration of necrotic pancreas with bacterial smear and culture.

**Pseudocyst:** A pancreatic pseudocyst develops in 10–15% of patients with acute pancreatitis. It requires **a minimum of 4 weeks** to develop after the acute attack. Basically, it is a collection of pancreatic fluid, which, if small enough, resolves spontaneously. A size **> 5 cm** suggests it may not resolve. If the pseudocyst persists > 3–6 months, it may require surgical drainage. Remove **enlarging** pseudocysts because they are associated with serious complications—especially fistula, pseudo-aneurysms, rupture, and hemorrhage. Rupture without hemorrhage = 15% mortality, while rupture with hemorrhage = 60% mortality! Consider this in a patient who is recovering normally and then suddenly gets worse. New data and most experts recommend intervening if the patient is symptomatic and not waiting to see if it resolves.

**Abscess:** A pancreatic **abscess** occurs **4–6 weeks** after onset of acute severe pancreatitis—in





## Quick Quiz

- What is the APACHE II score that indicates severe pancreatitis?
- How is pancreatic necrosis best confirmed?
- What masses may develop due to acute pancreatitis? What is their timeline and what is their treatment?
- Pseudocysts persisting for more than 3–6 months generally require what intervention?
- What is the 1<sup>st</sup> test in the workup of the etiology of acute pancreatitis?
- What is the clinical presentation of chronic pancreatitis?

which there is severe pancreatic necrosis. It may be seen as a “**soap bubble sign**” on upright abdominal x-ray. This is a very serious condition with fever and shock.

Diagnose pancreatic abscess with Gram stain of a **CT-directed percutaneous aspiration**, which is 90% accurate. This allows for immediate surgical debridement and drainage.

### Diagnosis of Pancreatitis

In working up the **cause** of acute pancreatitis, the first and often only test is gallbladder ultrasound to rule out gallstones. Diagnosis is often based mainly on history.

### Treatment of Acute Pancreatitis

With supportive care, ~ 90% resolve spontaneously within a few days. Patients must be made NPO for a variable period of time, but **NG suction** is generally **not** required. Provide vigorous IV crystalloid fluid replacement plus colloids as needed. **Enteral feeds** have been shown to be **superior to TPN** in maintaining nutritional status in patients with protracted acute pancreatitis.

Give systemic antibiotics if there is established infection or  $\geq 30\%$  pancreatic necrosis. (Note: The 2007 AGA guidelines support antibiotics with necrosis; the 2006 ACG guidelines do not.) Imipenem or meropenem are currently recommended.

Watch for antibiotic-associated fungal infections.

### Pearls of Acute Pancreatitis

If the amylase is still elevated after 10 days, think of something else going on, such as a leaking pseudocyst. With large fluid collections, consider a disrupted pancreatic duct leaking fluid. This can be treated by ERCP with stenting of the duct.

Recurrent acute pancreatitis with no evidence of gallstones or alcohol abuse may be due to **microlithiasis**; so, consider an elective cholecystectomy.

Gastric varices in the absence of esophageal varices occur only in **splenic vein thrombosis**, which is a complication of both severe **acute** pancreatitis and **chronic** pancreatitis.

ERCP is **not** done acutely **unless** a patient has cholangitis and sepsis. Use MRCP after the acute period to diagnose suspected common duct stones; e.g., the bilirubin is  $> 2.5$  and rising or the ultrasound shows a dilated common duct. Do therapeutic ERCP to treat ductal obstructions found on MRCP. Perform cholecystectomy ASAP after gallstone pancreatitis—after the inflammation has resolved.

Criteria for resumption of oral feeds in acute pancreatitis:

- Bowel sounds present and passing flatus/stools
- Not requiring narcotics
- Patient is hungry and wants to eat!

Question: What conditions can cause abdominal pain with an elevated **amylase**? Answer: Acute pancreatitis, acute cholecystitis, intestinal infarction, diabetic ketoacidosis, perforated ulcer, salpingitis, and ectopic pregnancy. Other causes of hyperamylasemia are increased salivary amylase and macroamylasemia (benign condition due to a low urinary excretion of amylase).

## CHRONIC PANCREATITIS

### Overview

In developed countries, chronic pancreatitis is usually (60–70%) a result of chronic alcohol ingestion—typically  $> 10$  years. Next in frequency is idiopathic (30%), and about 10% are rare hereditary disorders (lack of cationic trypsinogen activator inhibitor, SPINK abnormality) and other causes such as cystic fibrosis, pancreas divisum, tumor, and hyperparathyroidism. Autoimmune pancreatitis is a newly described, rare disorder that accounts for  $< 1\%$  of cases (see [page 1-43](#)).

Chronic pancreatitis has an initial, asymptomatic phase, followed by recurrent bouts of abdominal pain. Late in the disease, when  $> 80\text{--}90\%$  of the endocrine and exocrine pancreatic function is lost, patients develop **steatorrhea** and **diabetes**. The fecal fat in late-stage patients is higher than with other disorders—it may be  $> 100$  g/day. More than 40 g/day is highly suggestive of chronic pancreatitis. 1/3 of patients with chronic pancreatitis develop diabetes. Chronic pancreatitis also increases the risk of pancreatic cancer 2-fold—not enough to support screening.

## Diagnosis of Chronic Pancreatitis

The classic diagnostic triad for **chronic** pancreatitis is:

- 1) Pancreatic calcification
- 2) Diabetes
- 3) Steatorrhea

But this triad is present in < 20% of cases and usually is found only during late-stage disease.

Diagnosis can be difficult, so begin evaluation with simple, noninvasive tests that detect advanced forms of chronic pancreatitis. **First, get a CT of the abdomen**—if the pancreas is calcified, **or** if the pancreatic duct is dilated, **or** if the pancreas is atrophic, you have made the diagnosis of chronic pancreatitis!

Initial tests used in the diagnosis of chronic pancreatitis:

- **Abdominal CT** has 80–85% sensitivity and specificity and is the current initial **procedure of choice**.
- **Endoscopic ultrasound** (EUS) is very sensitive and may be the best test yet, **but** it requires a very skilled gastroenterologist. It is the procedure of choice in some centers.
- Abdominal U/S.
- Flat plate of the abdomen showing pancreatic calcification (only 30% sensitivity).
- Secretin stimulation test (see below).

Follow-up tests. If results from the tests above are negative, and you still have suspicions, do either magnetic resonance cholangiopancreatography (MRCP; preferred) or ERCP:

- MRCP is accurate in diagnosing chronic pancreatitis **without** the risk of causing pancreatitis (unlike ERCP, below). MRCP additionally visualizes the biliary tree and can also be useful in cases of suspected bile duct stones or other biliary diseases like PSC. MRCP is the preferred 2<sup>nd</sup> level test and some centers advocate secretin-stimulated MRCP.
- ERCP may induce pancreatitis (5–20%). The only advantage ERCP has over MRCP is the potential for endoscopic removal of **calcific stones**, which may be located within the duct and, hence, can be reached with the endoscope.

Both MRCP and ERCP can show **large** duct disease **and** **small** duct disease. With large duct disease, the pancreatic duct has stenoses and dilations, which visualize as an irregular **“chain of lakes.”**

Dilation of the common bile duct can be caused by chronic pancreatitis but also by pancreatic cancer. Either can compress the downstream portion of the common bile duct as it passes through the head of the pancreas.

The **secretin test** is the most sensitive test for pancreatic function; however, it is complicated, so it is usually performed only in major medical centers, and only when there is still a high “index of suspicion” after negative 2<sup>nd</sup> level tests. (This does vary—in some places with ready access, it is done before ERCP.) In this test, IV

infusion of secretin (+/– cholecystokinin [CCK]) causes a direct stimulation of the pancreas. Duodenal pancreatic secretions are then measured via a duodenal catheter. The bicarbonate concentration should be > 80 mEq/L. CCK stimulates lipase, amylase, trypsin, and chymotrypsin, all of which can be measured. An endoscopic secretin test is also now available.

## Complications of Chronic Pancreatitis

A major complication is persistent and severe abdominal pain. In this setting:

- Rule out continued EtOH use.
- Rule out pseudocyst.
- Do MRCP, EUS, or ERCP (least preferred) to define duct anatomy.
- Try high-dose pancreatic enzymes to shut off the enteropancreatic (intestine-pancreas) axis.

Pancreatic cancer develops in 4% of patients with chronic pancreatitis > 20 years.

Complications of chronic pancreatitis include gastric varices (from splenic vein thrombosis), B<sub>12</sub> malabsorption, jaundice, pleural effusion, and brittle diabetes mellitus. The **only** skin involvement is tender red nodules from fat necrosis; this is uncommon, but can simulate erythema nodosum.

The diabetes associated with chronic pancreatitis is **different** from the usual DM. It occurs when > 80% of the pancreas is destroyed. There is a decrease in production of insulin **and** glucagon.

Because the pancreas is producing so little **glucagon**, the patient is **very prone to hypoglycemia**. Therefore, less stringent control of **hyperglycemia** is recommended—to decrease the chance of life-threatening hypoglycemia.

These patients do **not commonly develop** retinopathy and nephropathy associated with the usual DM. They commonly have neuropathy, but it is more likely caused by alcoholism and/or malnutrition.

## Treatment of Chronic Pancreatitis

Treatment includes:

- Pancreatic enzymes (a minimum 20,000–30,000 units of lipase per meal)
- Decreasing dietary fat
- Adding **medium**-chain triglycerides to the diet

Pancreatic enzymes must either have an enteric coating or be given with antacids/H<sub>2</sub> blockers because gastric acid destroys enzymes. Alcohol consumption must be avoided. Discontinuation of smoking is very important because smoking **accelerates** the development of pancreatic calcification and makes pain management more difficult.

Analgesia is sometimes required. Most try a short-term opioid with amitriptyline. There is no therapy proven to show benefit if the pain persists.



## Quick Quiz

- What is the classic diagnostic triad for chronic pancreatitis?
- What is the preferred initial test used in the workup of chronic pancreatitis?
- When is ERCP considered over MRCP as a 2<sup>nd</sup> level test in the workup of chronic pancreatitis?
- What are the classic symptoms of pancreatic carcinoma?
- How is pancreatic cancer treated if there are metastases? Without metastases?
- When is ERCP indicated in pancreatic cancer?

## AUTOIMMUNE PANCREATITIS

You should know this entity, even though it occurs in < 1% of cases of chronic pancreatitis. It is interesting in that its presentation often simulates cancer of the pancreas.

What to know:

- 70% present with obstructive jaundice (simulating cancer of the pancreas).
- CT can show a mass in the head of the pancreas (again simulating cancer) or diffuse enlargement.
- There may be bile duct and pancreatic duct strictures.
- **Serum IgG4** level is usually  $\geq 2\times$  normal.

Histology shows a dense lymphoplasmacytic infiltrate. Treatment is corticosteroids.

## PANCREATIC NEOPLASMS

### Pancreatic Cancer

Pancreatic cancer is astonishingly aggressive. 80% of patients present with advanced disease. Heavy smokers have 2x the normal risk. Other risk factors include DM, pancreatic cancer in 2 first-order relatives, hereditary pancreatitis, and chronic pancreatitis.

Patients usually present with some combination of **jaundice**, unexplained upper **abdominal pain**, and/or **weight loss**.

Where the cancer is located in the pancreas affects presenting signs and stage:

- Head: **Painless** jaundice tends to be the presenting sign with early-stage cancers of the **head** of the pancreas.
- Body and tail: These patients are more likely to present with pain and weight loss (jaundice in only ~ 30%) and with the cancer at a much more advanced stage.

**Pain** and **weight loss** are indications of advanced disease. The pain typically has a gnawing quality, is not cured by eating, and occasionally radiates to the back.

Diagnosis is made using helical CT, CT angiography, endoscopic ultrasound (EUS)-guided FNA biopsy, and laparoscopy. Note: There is some controversy concerning FNA biopsy possibly seeding the tumor cells locally.

The most-used serum marker is the concentration of cancer-associated antigen 19-9 (**CA 19-9**).

Treatment of pancreatic cancer: **Resection** is the only hope for cure.

Most common reasons for being unresectable:

- Distant metastases
- Local invasion of major vessel (portal vessel or superior mesenteric vein or artery)

Basically, if the patient is a surgical candidate, the mass is in the **head** of the pancreas, and the cancer appears resectable, do a pancreaticoduodenectomy (Whipple resection). Lymph nodes are also checked—at which time you find out if they are node-negative or node-positive.

There is a modest survival benefit (survival increased 3+ months) with specific chemoradiotherapy (especially with 5FU or gemcitabine).

If noninvasive workup shows that the cancer has already metastasized, **avoid** surgery—provide supportive care or give experimental chemo (especially gemcitabine) only. Place a **stent** using ERCP to palliate biliary obstruction. This is the **only** time you use ERCP for pancreatic cancer.

Post-surgical prognosis: 5-year survival is 30% for node-negative and 10% for node-positive.

### Glucagonoma

A glucagonoma is a glucagon-secreting, alpha-cell tumor of the pancreas that causes a unique set of clinical findings. These are very distinctive:

- Scaly **necrolytic erythema**
- Weight loss
- Anemia
- Persistent **hyperglycemia**
- Plasma glucagon (by RIA) usually > 1,000 pg/dL

### Insulinoma

Insulinoma is a very rare, insulin-secreting beta-cell tumor of the pancreas. This is covered in the Endocrinology section, Book 4, under Hypoglycemia.

## Gastrinoma

Gastrinomas are discussed under ZES on [page 1-14](#). Most (50%) are found in the duodenum, 24% in the pancreas. This diagnosis is likely when the serum gastrin is  $> 500$  in a patient who is able to secrete gastric acid (not on PPI, no prior peptic ulcer surgery).

## VIPoma

VIPomas are tumors that secrete vasoactive intestinal peptide (VIP). 2/3 occur in the pancreas, and  $> 1/2$  of these are malignant. They cause a **profuse secretory diarrhea** ("pancreatic cholera"). Diagnosis: increased serum VIP level and hypokalemia.

# BILIARY SYSTEM

## CHOLELITHIASIS

### Overview

Cholelithiasis is widespread—20% of women and 8% of men—and usually asymptomatic. It is **not** associated with hypercholesterolemia.

The pathophysiology of cholelithiasis involves 1 or more of the following 3 factors:

- 1) Abnormal bile secreted by the liver (lithogenic—supersaturated with cholesterol)
- 2) Accelerated nucleation of microcrystals to macrocrystals
- 3) Defective gallbladder emptying

Cholelithiasis has been associated with obesity, oral contraceptive use, clofibrate treatment, and ileal disease or resection. 80% of gallstones are composed of radiolucent cholesterol; the rest are bile pigment gallstones.

Profile for **cholesterol** stones: rapid weight loss in obese patient (these stones prevented by aspirin or ursodeoxycholic acid), Native American, octreotide use.

Profile for **pigment** stones: ileal resection (as in Crohn disease), sickle cell disease, or anything else that causes hemolysis; e.g., *Clonorchis sinensis* (biliary dwelling trematode).

Symptoms: RUQ pain lasting 20–60 minutes—especially after a fatty meal. But fatty food intolerance is a very **nonspecific** finding.

### Diagnosis of Cholelithiasis

To detect the presence of stones, do an **ultrasound** (90% sensitive). A normal ultrasound in the presence of normal bilirubin and liver enzymes is sensitive for excluding common duct stones. If the ultrasound is technically inadequate, consider MRCP or oral cholecystogram. The usual procedures used for diagnosing common duct obstruction are MRCP, ERCP, and transhepatic cholangiography.

The HIDA scan (cholescintigraphy) is the best test for confirming acute **cystic** duct obstruction (i.e., acute cholecystitis) by imaging of the bile duct but not the gallbladder, although ultrasound has characteristic findings of acute cholecystitis.

Note: About half of pigment stones are radiopaque, whereas cholesterol stones never are.

### Treatment of Cholelithiasis

If the patient has gallstones and is **symptomatic**, do an elective cholecystectomy because 70% of these patients have recurrent symptoms if not treated.

If a patient has gallbladder stones but is asymptomatic, no treatment is indicated because only 20% subsequently develop symptoms within 10–20 years. Don't mistake symptoms of reflux for that of cholelithiasis, even if you incidentally find stones in the gallbladder.

Supplemental oral bile acid (ursodeoxycholic acid) may be used in the treatment of gallstones for those who are too ill to have surgery or refuse surgery. Lithotripsy can be effective, but few centers have expertise.

**Acalculous** cholecystitis occurs only in **seriously ill** patients; e.g., major trauma, burns, after major surgeries. Diagnosis may be assisted by ultrasound or CT showing no stones, but a large, tense, often thickened gallbladder with pericholecystic fluid (or no stones and a HIDA scan showing cystic duct obstruction). Treatment is cholecystectomy, but cholecystostomy (percutaneous drainage) can be done if the patient is too sick for surgery.

### Common Duct Stones

Alkaline phosphatase and bilirubin levels usually do **not** increase in typical gallbladder cases because the gallstones block only the exit to the gallbladder. **Increasing levels** of alk phos and bili (bilirubin  $> 4$  mg/dL) suggest a common duct stone. Consider common duct stones in the gallbladder patient with increased alk phos and bili or the post-cholecystectomy patient with persistent pain. Common duct blockage also can cause cholangitis (below).

Common duct stones are removed by ERCP with *prn* endoscopic sphincterotomy.

## CHOLESTASIS

Cholestasis can be obstructive (as with common duct stones) or hepatocellular. In both cases, there is retention of the substances normally released into bile. In both cases, there are "cholestatic" LFTs with increased alkaline phosphatase and conjugated bilirubin with bilirubinuria. More on bilirubin on [page 1-59](#).

## CHOLANGITIS

Cholangitis is a complication of common bile duct blockage—caused usually by bile duct stone or cancer.



## Quick Quiz

- What are the 3 causative factors of cholelithiasis?
- What should you investigate in the patient who persists in having RUQ pain after cholecystectomy or with symptoms of cholangitis?
- What is the “hallmark” test for primary biliary cirrhosis? How do you confirm the diagnosis?

Acute cholangitis is suggested by the triad of biliary colic, fever and chills, and jaundice (Charcot’s triad). Suppurative cholangitis additionally has mental confusion, bacteremia, and septic shock.

Treatment is **parenteral antibiotics** and **biliary drainage**; antibiotics alone are not sufficient. When you suspect suppurative cholangitis, the best procedure for both diagnosis and treatment is **ERCP with endoscopic sphincterotomy** or surgery if ERCP is not available.

**Emphysematous** cholecystitis requires emergent laparotomy with cholecystectomy and antibiotics. In both suppurative cholangitis and emphysematous cholecystitis, the antibiotics must be effective against both **gram-negative** and **anaerobic** organisms. Do **not** use ceftriaxone—it can cause biliary sludge and has no (zero!) anaerobic coverage.

## PORCELAIN GALLBLADDER

X-ray showing a gallbladder with a **calcified outline** (“porcelain gallbladder”) suggests **cancer**, and an open cholecystectomy is indicated.

## PRIMARY BILIARY CIRRHOSIS

### Overview

Primary biliary cirrhosis (PBC): **slow** onset. **95% are women**—usually **middle-aged**. PBC is characterized by a nonsuppurative, progressive, destructive cholangiolitis. The bile ducts become chronically inflamed and eventually cause obstructive jaundice and liver cirrhosis.

The cause of PBC is unknown, but 70% have associated diseases of altered immunity (e.g., Sjögren’s, scleroderma, autoimmune thyroiditis, limited scleroderma), and the disease **does** run in families. **90%** have a positive **antimitochondrial antibody** test ( $> 1:40$ ), but degree of elevation does **not** correlate with severity of disease.

PBC patients who present with symptoms have **advanced** disease. Most patients present asymptotically or with **fatigue** and are worked up because of a **high alkaline phosphatase** noted on a liver enzyme screening. If they have symptoms, patients initially complain of **itching**—first in the palms and soles and later throughout the body.



Image 1-21: Jaundice in the patient with biliary cirrhosis



Image 1-22: Xanthelasmata

They later develop jaundice, hyperpigmentation, inflammatory arthropathy, keratoconjunctivitis and/or xerostomia, and accelerated osteoporosis. Patients can develop xanthomas and xanthelasma from associated hypercholesterolemia, but this does **not** convey increased risk of CAD (not an atherosclerogenic lipid pattern). (See [Image 1-21](#) and [Image 1-22](#).)

PBC is indolent, but relentlessly progressive. Symptomatic patients previously had a median survival of 7 years, and asymptomatic 10–16 years. These numbers are increasing significantly as patients are diagnosed earlier and all patients are treated with **ursodiol** (ursodeoxycholate; see Treatment on next page).

When the bilirubin increases to  $> 2$ , the disease **accelerates**. Most die soon after the bilirubin reaches 10 **unless** the patient undergoes liver transplantation.

Incidental discovery of a 2–5x increase in serum **alkaline phosphatase** has been the primary reason for the increase in PBC diagnoses. High levels of alk phos occur in up to 95% of patients with PBC.

Note: The **antimitochondrial antibody** test is the **hallmark** test for PBC. Even so, it is **not** a good indicator of the **severity** of PBC. The antimitochondrial antibody test is only **occasionally** positive in both autoimmune hepatitis and drug-induced chronic hepatitis; a high titer in a patient with autoimmune hepatitis suggests an overlap syndrome ([Table 1-8](#)).

### Diagnosis of Biliary Cirrhosis

Diagnosis is confirmed **only** with a **liver biopsy**, which may show granulomas; often it has nonspecific findings. PBC patients also have a high hepatic **copper** level (but so do those with primary sclerosing cholangitis and Wilson disease).



**Table 1-8: Serologic Markers in PBC and CAH**

|                       | Primary Biliary Cirrhosis | Drug-induced CAH* | Auto-immune CAH*          |
|-----------------------|---------------------------|-------------------|---------------------------|
| Antimitochondrial Ab  | 90–95% Positive           | occ Positive      | occ Positive (low titers) |
| Anti-Smooth muscle Ab | Negative                  | Negative          | Positive                  |
| Antinuclear Ab        | usually Negative          | Negative          | Positive                  |

\* chronic active hepatitis

### Treatment of Biliary Cirrhosis

**Ursodiol** (ursodeoxycholate—a synthetic bile acid) is the best proven treatment available for PBC. It improves LFTs and decreases symptoms, and it significantly **slows** progression of the disease. Patients who have a **biochemical response** to ursodiol (defined as a decrease in alk phos, AST, and/or bilirubin to much lower level at 1 year) have **dramatic slowing** of the progression.

Additionally, there is symptomatic treatment:

- Pruritus: cholestyramine
- Osteomalacia: vitamin D and calcium
- Malabsorption: medium-chain triglycerides and decreased dietary fat

Treatment has **no effect** on **late** disease.

For late disease, liver transplantation is the recommended treatment. It has been shown to significantly improve survival in late PBC. PBC is one of the most common disease indications for liver transplantation! Hepatitis C is the most common indication. The “**AAAABCs** of PBC” are: **A**ntimitochondrial **A**ntibody **A**ttack increases **A**lk phos and causes **B**iliary lesions and **C**irrhosis.

## PRIMARY SCLEROSING CHOLANGITIS

### Overview

Primary sclerosing cholangitis (PSC): also indolent. It primarily occurs in males (70%) with average age of 45.

PSC has a strong association with **colitis**—so it is **mainly** seen in ulcerative colitis (up to 75% of PSC patients have UC!) but can occur in Crohn disease involving the **colon**. It has no relation to the **severity** of colitis.

PSC occurs in 5% of UC patients and maybe 2% of Crohn patients. UC may precede the diagnosis of PSC, but not necessarily. So **all** PSC patients should have a colonoscopy.

Conversely, PSC may precede the diagnosis of UC; therefore, any UC patients with a persistent,  $\geq 2x$  increase in **alkaline phosphatase** should be screened for PSC.

Cause is unknown. Patients develop inflammation and sclerosis of the entire biliary tract (intra- and extrahepatic), leading to obstructive jaundice and eventually cirrhosis.

**Bilirubin** and **alkaline** phosphatase levels are elevated (cholestatic pattern). There is an elevated hepatic **copper** level (as in primary biliary cirrhosis and Wilson disease), but the antimitochondrial antibody is **negative**. The total protein level gives an idea of how much the disease has affected liver function.

Patients are initially asymptomatic but eventually, with advanced disease, develop weakness and fatigue, abdominal pain, itching, and jaundice.

8–15% of PSC patients develop **cholangiocarcinoma**. One-third have it when first diagnosed with PSC! Suspect if symptoms of PSC abruptly worsen. CA 19-9 is elevated in 80%.

### Diagnosis of Sclerosing Cholangitis

Diagnosis of PSC is made with **MRCP** (best), ERCP, or transhepatic cholangiography. These reveal irregularly narrowed bile ducts with small bile duct ballooning just prior to obstructions, producing the typical “**beaded**” appearance. With ERCP, if a dominant stricture exists, it can be dilated. Liver biopsy will show “onion skin” fibrosis in portal triads.

In small duct PSC, the extrahepatic and intrahepatic biliary system may be nondiagnostic, but **liver biopsy** abnormalities establish the diagnosis.

Secondary causes of sclerosing cholangitis must be ruled out. These include: bacterial cholangitis (stones or bile duct stricture), atypical anatomy (congenital or previous surgery), bile duct neoplasms, and AIDS-associated cholangiopathy.

### Treatment of Sclerosing Cholangitis

Treatment of PSC: The only sure treatment for PSC is a **liver transplant**—although colectomy cures ulcerative colitis, it does not change the course of PSC.

Know: High-dose ursodeoxycholic acid (UDCA, 20–25 mg/kg) was recommended in the past, but a 2010 guideline from the American Association for the Study of Liver Diseases now recommends **against UDCA** because of lack of efficacy and increased risk of adverse effects! If patients are already on UDCA because of past recommendations, some now recommend to **stop** it!

Remember: When a patient presents with jaundice and increased alk phos and has a history of chronic diarrhea or IBD, **especially** UC, rule out PSC with MRCP or ERCP!

Again, PSC: Sclerosing **C**holangitis, **c**olitis, high **c**holestatic bili and alk phos levels; negative antimitochondrial antibody. Abnormal magnetic or endoscopic retrograde cholangiopancreatography (MRCP, ERCP).



## Quick Quiz

- PBC: What is the best, proven treatment for early disease? For late disease?
- List the similarities and differences between PBC and PSC. These are commonly confused diseases. [Know!] What are the alk phos, bilirubin, hepatic copper, and antimitochondrial antibody tests in PBC and PSC?
- A patient presents with cholestatic jaundice and a history of IBD (or a history of chronic diarrhea). Which of the following do you include in your differential—PBC or PSC? Why?
- How do you confirm that a hepatitis B vaccine was immunogenic?

Table 1-9: PBC vs. PSC

|     | Sex    | IBD | Cancer                                | UDCA effective? |
|-----|--------|-----|---------------------------------------|-----------------|
| PBC | Female | No  | Rare                                  | Yes             |
| PSC | Male   | Yes | (UC) 8–15% risk of cholangiocarcinoma | No              |

### PBC vs. PSC

These two conditions are often confused because they have similar abbreviations and both affect the bile tracts and have high alk phos and elevated hepatic copper level. Both eventually cause obstructive jaundice and cirrhosis. (Hmm. Why the confusion?) To help remember the differences, drop the abbreviations and think:

- Biliary cirrhosis: 55-year-old woman named Hillary C. Roses with fatigue and pruritus. Antimitochondrial Ab+.
  - Sclerosing cholangitis: 45-year-old man with UC.
- Also review [Table 1-9](#).

## LIVER

### HEPATITIS NOTES

Regarding ALT (SGPT) and AST (SGOT), know:

- To remember that ALT is more liver-specific than AST, think of “L-L” (ALT-Liver):
- With alcoholic hepatitis, the AST:ALT is about 3:1 because the alcohol damages **mitochondria**, which then release the AST. Mitochondrial damage is less liver-specific.

- With viral hepatitis, the ALT is usually greater than the AST because its toxicity is more liver-specific. [Table 1-10](#) reviews the hepatitis serological tests.
- Nonalcoholic fatty liver disease (NAFLD) is also more liver-specific and has an ALT:AST ratio > 2:1.

Acute viral hepatitis has histologic characteristics of diffuse liver cell injury and swelling, increased macrophages, accelerated apoptosis (the normal programmed cell death is accelerated by viral hepatitis), and inflammatory periportal infiltrates (mostly lymphocytic).

Chronic viral hepatitis has histologic characteristics of interface hepatitis (formerly known as piecemeal **necrosis**) and **fibrosis**.

### EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS

#### Increased Transaminases

An abnormal laboratory value should be confirmed before ordering specific tests. To confirm, order a full set of liver biochemical tests, including alkaline phosphatase, total and direct bilirubin, albumin, PT, and CBC. If the transaminases are still elevated, order more specific tests for hepatitis A, B, and C—and tests for hemochromatosis to include iron studies and ferritin level.

#### Increased Alkaline Phosphatase

Remember that alkaline phosphatase comes from liver and bones. Gamma glutamyl transpeptidase (GGT) usually rises in parallel with alkaline phosphatase from the liver and should be checked in cases of increased alkaline phosphatase with normal bilirubin and transaminases. Generally, the next test is abdominal ultrasound to look for dilated biliary ducts or metastatic liver lesions. In appropriate patients, also order antimitochondrial antibody test (to screen for PBC).

### HEPATITIS B

#### Overview

The 5 main serological markers in hepatitis B are HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb ([Table 1-10](#) and [Table 1-11](#) on [page 1-48](#)).

**HBsAg:** There are 3 HBsAg+ proteins seen in the serum in patients with hepatitis B: one large, double-shelled 42 nm particle that is the **intact virion** and two smaller 22 nm spherical or rod-shaped protein particles that outnumber the large particle by up to 1,000 to 1! These 22 nm HBsAg+ particles are thought to be just excess viral coat protein. Having HBsAg means you are producing hepatitis B virus.

**HBsAb:** Finding HBsAb in the serum indicates past exposure to either hepatitis B virion or to the vaccine. Usually it indicates **immunity**.

Table 1-10: Hepatitis — Serological Tests

|                                | Anti-HAV IgM | Anti-HAV IgG | HBsAg   | Anti-HBs IgG | Anti-HBc IgG | Anti-HBc IgM | HBeAg | Anti-HDV |
|--------------------------------|--------------|--------------|---------|--------------|--------------|--------------|-------|----------|
| Acute hepatitis A              | +            | —            |         |              |              | —            |       |          |
| Previous HAV                   | —            | +            |         |              |              | —            |       |          |
| Acute HBV                      | —            | —            | + early | —            | —            | +            | +     | —        |
| Acute HBV—window               |              |              | —       | —            | —            | +            | —     | —        |
| Chronic active HBV             |              |              | +       | —            | +            | —            | usu + | —        |
| Remote HBV (immune)            |              |              | —       | +            | +            | —            | —     | —        |
| Vaccinated (immune)            |              |              | —       | +            | —            | —            | —     | —        |
| Acute hepatitis D (w/acute HB) |              |              | + early | —            | —            | +            | +     | +        |
| Acute hepatitis D (w/CAH)      |              |              | +       | rarely       | +            | —            | usu + | +        |

**HBcAg** is the inner shell protein of the above 42 nm virion. This protein is retained in the hepatocyte until it is covered with HBsAg+ nucleocapsid outer shell, which will then incorporate the DNA. Free **HBcAg does not circulate** in the serum. Antibody to HBcAg appears early in the disease (initially IgM, then IgG) and persists for life, so **HBcAb IgG** is the best marker for **previous** exposure to HBV. However, it will not distinguish between active or “cured” infection.

**HBeAg** is a soluble protein made from the same gene as HBcAg, but, unlike HBcAg, HBeAg **is** secreted from the hepatocytes and circulated in the serum. HBeAg correlates with the **quantity of intact virus** and, therefore, with **infectivity** and liver **inflammation**. The HBe antibody (**HBeAb**) appears several weeks after the illness. Detecting HBsAg **and** HBeAg indicates active virions and high infectivity (more so than HBsAg+ and

HBeAg–). The tests for HBeAg and HBeAb are often not available locally.

Confused? Reread the highlighted text and remember:

- **HBsAg+** means a patient is making hepatitis B virus. It could be low levels or very high. It can be acute or chronic.
- **HBeAb+** almost always means the patient is “cured” of previous hepatitis B infection or, if this is the only marker (specifically no IgG HBeAb), then the patient was vaccinated.
- **HBeAg+** means the patient is **highly infectious** and actively making hepatitis B virus.

Hepatitis B is the **only** hepatitis virus composed of **DNA**. Incubation period is 1–6 months. It is transmitted by contaminated serum or blood products. Once infected, the

Table 1-11: Interpretation of Hepatitis B Tests

| HBsAg | Anti-HBc | Anti-HBs | Interpretation                                                                                                                                               |
|-------|----------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| +     | —        | —        | Acute Infection                                                                                                                                              |
| +     | +        | —        | 3 possibilities: 1) Acute infection (IgM anti-HBc)<br>2) Chronic Hep B (high ALT, IgG anti-HBc)<br>3) Inactive carrier (normal enzymes, IgG anti-HBc)        |
| —     | —        | +        | 2 possibilities: 1) Remote infection<br>2) Immunized                                                                                                         |
| —     | +        | +        | Remote infection                                                                                                                                             |
| —     | +        | —        | 3 possibilities: 1) Window disease<br>2) Remote infection<br>3) False positive                                                                               |
| +     | +        | +        | More than 1 infection; e.g., IV drug user or renal dialysis patient with both acute and chronic hepatitis B (infected with different strains of hepatitis B) |



## Quick Quiz

- Regarding HBsAg, HBcAg, and HBeAg: Which is the best marker for infectivity? Which is the best marker for past infection?
- What is the “window” period for hepatitis B infection?
- Polyarteritis nodosa is associated with which hepatitis virus?
- Are hepatitis B vaccines safe for pregnant patients?
- Know Table 1-10 through Table 1-13.

1<sup>st</sup> marker detectable in the serum is the antigen HBsAg. This is followed by the appearance of **antibody** to the core antigen. After HBsAg becomes undetectable, there is a period of weeks to months before the HBsAb antibody becomes detectable. This is called the “**window**,” and you must perform an HBcAb IgM test during this period to confirm acute hepatitis B (Figure 1-5 and Table 1-11).

Hepatitis B is strongly associated with **polyarteritis nodosa** (PAN). The surface antigen is found in 20–30% of these patients. It appears that the hepatitis B infection precipitates an autoimmune reaction resulting in PAN.

Clinical: First, there are prodromal constitutional symptoms, which typically resolve at the time jaundice becomes apparent. Occasionally (10–15%), the prodromal symptoms are **serum sickness-like** with fever, arthritis, urticaria, and angioedema. This seems to be caused by circulating immune complexes (especially “HBsAg—HBsAb” immune complex) activating the complement system. With the onset of jaundice, the patient usually feels much better but may have liver swelling and tenderness and cholestatic symptoms.

Removal of HBV is **T-cell-mediated**, and the only purpose of HBsAb is to prevent **reinfection**.

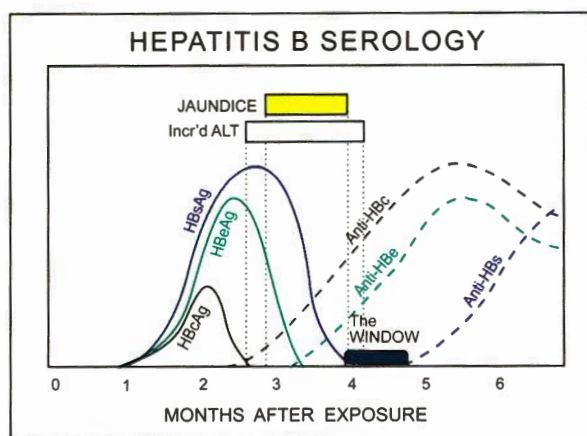


Figure 1-5: Hepatitis B Serology vs. Time after Exposure

Hepatitis B immune globulin (HBIG; HBsAb) provides some protection against hepatitis B, although it appears to only decrease the severity of illness rather than protect the patient from disease.

HBIG is effective both as short-term prophylaxis and when given in early infection.

### Hepatitis B Vaccines

The 2 hepatitis B vaccines are composed of HBsAg. They are equally effective and are **safe for pregnant patients**. It is best if the hepatitis B vaccine is given **before** the patient is exposed to HBV. 95% of immuno-competent patients develop antibodies, whereas only about 50% of dialysis patients do (even though dialysis patients also are given a much higher-dose vaccine than other adults are).

Because these vaccines are **surface** antigens, to ensure effectiveness after the course of vaccine has been given, check for HBsAb which develop in response to this antigen—there will be **no** HBcAb.

Indications for hepatitis B vaccine in adults include persons engaging in high-risk sexual behavior, those with chronic liver disease, persons with HIV infection, and dialysis patients.

### Hepatitis B Treatment Scenarios

Scenarios:

- Give a newborn of a mother with hepatitis B both hepatitis B immune globulin (HBIG) and hepatitis B vaccination. There is a 5–10% transplacental transmission of HBV.
- If an asymptomatic patient has HBsAg in the serum, it means **either** the patient is a carrier **or** the patient has early hepatitis B—so initial action is only to follow closely. (Once the patient is **infected**, neither vaccine nor HBIG helps.)
- Close contacts of a patient with acute HBV infection should be given HBIG followed by a complete course of HBV vaccinations. This includes sexual contacts and household contacts of the patient. Pregnant women are treated the same.

Note: Several months after an episode of hepatitis B infection, check for loss of HBsAg and HBV-DNA to ensure that it has not become a chronic infection.

### Chronic Hepatitis B

The likelihood of developing **chronic** HBV is **inversely** related to **age**. Chronic HBV occurs in 90% of infants infected at birth, 25–50% in children age 1–5 years, and **5%** in older children and adults. Note that comorbid conditions (hemochromatosis, AIDS/HIV, alcohol) worsen course and response to treatment.

There is now universal preschool vaccination in the U.S. Overall, < 1% of patients with hepatitis B develop fulminant hepatitis, but 5–7% develop chronic carrier states.

There are 2 types of hepatitis B carrier states:

- 1) Inactive carrier state (asymptomatic with **normal** liver enzymes)
- 2) Chronic active hepatitis B (abnormal enzymes)

A **liver biopsy** is usually required to confirm the diagnosis of chronic hepatitis B.

Patients with **inactive** carrier states **can** develop severe exacerbations of hepatitis B if they become **immuno-compromised**. For example, a woman with breast cancer who also has an inactive carrier state with hepatitis B is to be started on chemotherapy. What other drug is given? **Lamivudine** (or lamivudine + adefovir) is given with her chemotherapy to blunt viral replication.

Chronic hepatitis B is a serious illness—it often progresses to **cirrhosis** and is strongly associated with **hepatocellular cancer** (HCC; 2% conversion per year). Lifetime risk for HCC is 20%.

Screen for HCC every 6 months with abdominal **ultrasound** (just as we do with chronic hepatitis C and alcoholic liver disease). **Helical CT** or **MRI** can also be used (more sensitive but much more expensive).

Note: Previously, an alpha-fetoprotein test was also used for screening, but the 2010 AASLD HCC Guideline notes that alpha-fetoprotein does **not** have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This new guideline supports an ultrasound-alone strategy.

### Treatment of Chronic Active Hepatitis B

#### Who Should Be Treated

Use HBV DNA, ALT, HBeAg, and degree of cirrhosis to determine when to treat.

Treatment is recommended for those with **HBV DNA > 20,000** and **ALT > 2 x ULN**:

- Treatment is started immediately for HBeAg–.
- Treatment is delayed 3–6 months for newly diagnosed HBeAg+ patients to see if seroconversion takes place.

The presence of **cirrhosis** requires less HBV DNA to initiate treatment. Treat:

- Compensated cirrhosis when HBV DNA > 2,000
- Decompensated cirrhosis when HBV DNA > 200

See **Table 1-12** for treatment options for chronic active hepatitis B.

Liver transplantation is the only treatment for end-stage liver disease. The HBV recurs in the transplanted liver, but an antiviral treatment program can help.

### HEPATITIS A

Hepatitis A is an **RNA** virus. It is easily transmitted by the fecal-oral route—usually via food or water. It can be sexually transmitted. There is **no** transplacental transmission! There are **no** carrier or persistent states, although, occasionally, these patients get **prolonged cholestasis** (with increased bili and alk phos) for up to 4 months. Incubation period is 15–50 days. See **Figure 1-6**.

Symptoms are unusual in children and very common in adults (70%). Complications are rare; there is ~ 1% chance of fulminant hepatitis. Immune globulin (IG) is good prophylaxis **only** against HAV (use HBIG for hepatitis B).

Diagnosis of acute infection: high titers of anti-HAV IgM in serum. (IgG indicates only a previous infection.)

The incidence of hepatitis A has fallen dramatically due to immunization.

Hepatitis A vaccine (Havrix® and Vaqta®) is for use in patients > 1 year of age and is given as 2 doses, 6+ months apart. Virtually all of those completing the series develop protective antibodies (anti-HAV IgG). Trends, based on what is now known of the antibody levels, suggest protection for up to 20 years in those who complete the series. If completion of the 2-dose series is delayed, there is **no** need to start the series over again.

**Table 1-12: Treatment of Chronic Active Hepatitis B**

| Treatment   | Benefits                                                                   | Disadvantages                                                              | Used for                                                               |
|-------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------|
| Interferon  | Limited duration of therapy; 35% complete remission; No resistance; Potent | Side effects may be severe; Contraindicated in decompensated liver disease | Primary treatment for young patients and women contemplating pregnancy |
| Entecavir   | Low drug resistance                                                        | Potent antiviral                                                           | Primary treatment                                                      |
| Lamivudine  | Great safety profile, even in pregnancy                                    | High rate of drug resistance                                               | Primary treatment                                                      |
| Adefovir    | Active against lamivudine-resistant HBV                                    | Low viral suppression                                                      | Lamivudine-resistant HBV                                               |
| Telbivudine | Slightly more potent than adefovir and entecavir                           | Same resistance profile as lamivudine                                      | Not used much                                                          |



## Quick Quiz

- With what coinfection can hepatitis A become fulminant?
- What test confirms that a previous hepatitis C infection did not become chronic?

Indications for use of HAV vaccine:

- High-risk sexual behavior (see hepatitis C section).
- IV drug use.
- Universally recommended for all > 1 year of age.
- Chronic liver disease.
- Travel in high-risk countries.
- HAV vaccine is also given to all patients with chronic hepatitis B and hepatitis C; if these patients get hepatitis A, it can be fulminant.
- Also now (since 2007) recommended for post-exposure prophylaxis instead of immune globulin.

Note: Onset of jaundice is **3 weeks** with hepatitis A and **3 months** with hepatitis B—an important diagnostic clue!

## HEPATITIS C

### Overview

Hepatitis C: single-strand **RNA** virus. It is now one of the most common liver diseases in the U.S. [Know this section well!] It is second only to NAFLD (nonalcoholic fatty liver disease, see [page 1-55](#)). Hepatitis C has blood-borne transmission and was the cause of 90% of transfusion-associated hepatitis prior to the early 1990s. Since then, especially with the 2<sup>nd</sup> generation **HCV Ab** assays, the incidence of transfusion-related hepatitis has become **very rare**.

Hepatitis C genotypes are 1a, 1b, 2, 3, 4, and 5. Genotypes influence response to treatment. Most HCV

infections in the U.S. (> 70%) are **genotype 1**, which happens to be **less** responsive to treatment than the other genotypes.

Increased risk for hepatitis C:

- Especially IV drug abusers; common in prisons
- High-risk sexual behavior: with STD, sex with prostitutes, > 5 sexual partners per year
- Blood transfusion before 1990
- Tattoos, body piercing
- Shared razors and toothbrushes
- Snorting cocaine
- Needle stick injuries
- Renal dialysis personnel

The hepatitis C “rule of 2s”:

- 2% of U.S. population
- 2% risk of needlestick transmission (though some say 5%+)
- 2% risk of neonatal transmission
- 2% risk of spousal transmission
- 2% cirrhotics with hepatitis C develop hepatoma each year

### HIV and Hepatitis C

In the U.S., 30% of patients with HIV are coinfecting with HCV. These patients progress faster to cirrhosis than those with HCV alone. Best treatment of HCV for HIV-infected patients is combination therapy: pegylated interferon and ribavirin with referral to a specialist for treatment.

### Extrahepatic Disease with Hepatitis C

Extrahepatic disease includes:

- Small vessel vasculitis with glomerulonephritis and neuropathy
- Mixed cryoglobulinemia (discussed under Chronic Hepatitis C, next page)
- Porphyria cutanea tarda (PCT)

PCT is associated **only** with hepatitis C (and not B). So, skin blisters? Think C!

### Serology and Hepatitis C

Within 2–4 months after an episode of hepatitis C, **recheck** for loss of **HCV RNA** (PCR) to ensure that the disease has not become chronic. Note: This HCV RNA test is not quantitative—but it is sensitive and can determine if there are more than 200 IU/mL of HCV RNA present.

In a person positive for HCV Ab, check for active virus with HCV-RNA. This is necessary because the HCV Ab does **not** confer immunity (as does the HBV antibody to HB).

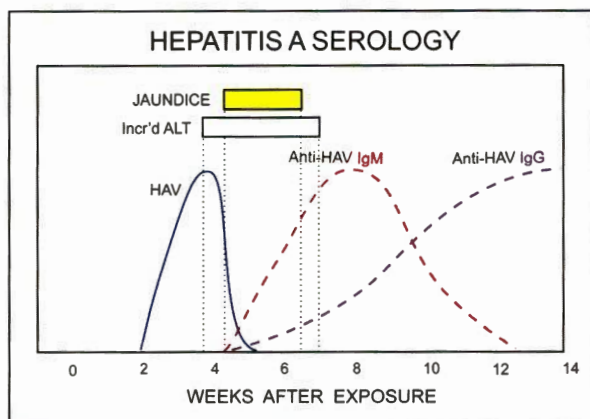


Figure 1-6: Hepatitis A Serology vs. Time after Exposure

## Chronic Hepatitis C

Whereas < 5% of adults with hepatitis B develop chronic disease, 70–80% of acute HCV infections become **chronic**! Hepatitis B has **high** virus counts, whereas hepatitis C has **lower** virus counts, as evidenced by hepatitis C viral RNA (units/mL).

These low virus counts are consistent with the more **insidious** nature of hepatitis C:

- Only 25% of acute infections are symptomatic.
- HCV infection has an increased likelihood to become chronic.
- The chronic form is relatively benign. (25% are only carriers; 50% have no symptoms but have abnormal LFTs; 25% have chronic active disease with symptoms.)
- Low rates of sexual transmission are seen in monogamous couples—2% after 10–20 years! This is low but it does occur—so safe sex **is** required! Sexual transmission increases with multiple sexual partners.
- Needlestick transmission from a known infected patient is 2–6%.
- Transplacental infection can occur (~ 2%), although this is less of a risk than for hepatitis B (5–10%).

70–80% of patients infected with HCV develop chronic hepatitis, and about 25% of these get end-stage cirrhosis after 20–25 years! And 1–4% of patients with cirrhosis develop **hepatocellular cancer (HCC)** each year (similar to chronic active HBV).

Screen for HCC every 6 months with abdominal **ultrasound** (as also done with hepatitis B and alcoholic cirrhosis). **Helical CT** or **MRI** can also be used (more sensitive but much more expensive).

Note again: Previously, alpha-fetoprotein test was also included, but the 2010 AASLD HCC Guideline notes that alpha-fetoprotein does **not** have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This new guideline supports an ultrasound-alone strategy.

Chronic HCV infection has become the #1 cause of liver transplants in the U.S.

Vaccinate all patients with chronic hepatitis C against hepatitis A and B. Giving the combination HAV+HBV vaccine is the simplest method, and either the routine or accelerated immunization schedule is reasonable.

**Mixed** cryoglobulinemia is **strongly** associated with chronic HCV infection (55% of those with chronic HCV). It presents as a small vessel (leukocytoclastic) vasculitis with a rash consisting of “palpable purpura” or “crops of purple papules.” Mixed cryoglobulinemia may much less often be seen in chronic hepatitis (15%), other chronic liver diseases (30%), and connective tissue diseases.

## Treatment of Chronic Hepatitis C

If the patient has **chronic** hepatitis C and elevated liver enzymes, the current standard treatment is the **combination** of the following:

- Pegylated INF- $\alpha$  (weekly injections—see hepatitis B), which also decreases risk of HCC
- Oral ribavirin

Measure response to treatment by following **HCV-RNA**; if no response at 12 weeks—seen as a decrease in HCV-RNA by 2 log units—discontinue therapy. For those who respond, if the HCV is genotype 1, treat for 1 year; if it is genotype 2 or 3, treat for 6 months.

Notes on treatment:

Medications have no role in end-stage cirrhosis.

Ribavirin therapy can be complicated by **hemolytic anemia**, but if mild, this is not an indication to stop treatment; rather, give epoetin (erythropoietin, recombinant). However, ribavirin is relatively contraindicated in cardiac patients with borderline hematocrit levels.

Caution using INF- $\alpha$  in the patient with a history of depression.

New protease inhibitors (telaprevir; and others now in trials) may change standard HCV treatment in the future.

## HEPATITIS D

Hepatitis D is an RNA virus that requires a **coexistent** hepatitis B virus infection for the hepatitis D to become pathogenic. It is usually found in IV drug abusers and high-risk HBsAg carriers (HBV DNA levels > 10 million). It usually does not make an acute HBV infection much worse, but, if acquired as a superinfection in an HBV carrier, the infection is frequently very severe. If acquired acutely, HDV does not increase risk of chronic hepatitis B. Immunity to hepatitis B implies immunity to hepatitis D. Diagnosis: anti-HDV IgM.

## HEPATITIS E

Hepatitis E: single-strand RNA virus. Fecal/oral spread (like HAV). Found in the Far East, Africa, and Central America, usually due to contamination of water supplies after monsoon flooding. Like hepatitis A, no chronic form is known.

Unlike hepatitis A, hepatitis E carries a very high risk for fulminant hepatitis in the 3<sup>rd</sup> trimester of pregnancy—with a 20% fatality rate. In a **traveler** with acute hepatitis and **negative standard serology (Hep A, B)**, think of hepatitis E.

## HEPATITIS G

Hepatitis G is blood-borne, like hepatitis B and C. Mode of transmission is not well defined but likely is similar to HCV. There is evidence of infection in 1.5% of



## Quick Quiz

- With which chronic hepatitis infection is mixed cryoglobulinemia strongly associated? How does it present?
- Which virus does hepatitis D require to replicate?
- Hepatitis E is associated with which risk factor?
- What test has an 80% rate of specificity for autoimmune hepatitis?
- What is the treatment for autoimmune chronic hepatitis?

blood donors. It causes < 0.5% of community-acquired hepatitis. There is no evidence that HGV causes chronic liver disease.

## CHRONIC HEPATITIS

### Overview

There are quite a few causes of chronic hepatitis as shown in Table 1-13. We have already discussed chronic hepatitis B and C. We'll cover the other causes here.

### Autoimmune Chronic Hepatitis

Type 1 autoimmune hepatitis usually has an insidious onset and is most often found in young women. Type 2 is a childhood disease and will not be discussed. All the following concerns Type 1 only.

50% of adult patients with autoimmune chronic hepatitis also have other disorders of altered immunity; e.g., thyroiditis, Coombs+ anemia, and ITP.

Autoantibodies are common; affected patients with Type 1 may have a positive ANA (+/- anti-dsDNA), anti-smooth muscle antibodies (anti-SMA), anti-actin antibodies (AAA), p-ANCA, and anti-soluble liver antigen (anti-SLA).

ANA is the **most sensitive** but is the **least specific**.

**Anti-smooth muscle antibody** (anti-SMA) is **more specific** than ANA, and it is positive in ~80% of patients with Type 1 autoimmune hepatitis. It is occasionally seen as an overlap syndrome with PBC or PSC. Refer to Table 1-8.

**Anti-actin antibody** (AAA) test is now commonly available and has, in some labs, replaced the anti-SMA test because it is even more **specific** and **sensitive**.

**Anti-SLA** is the **most specific** for Type 1 but **not sensitive**.

You can also check for antimitochondrial antibody—it is only occasionally slightly positive, but high titer occurs in primary biliary cirrhosis (PBC) and indicates an overlap syndrome. Remember, as a rule of thumb, PBC occurs in middle-aged women, autoimmune hepatitis occurs in **young** women, and PSC in middle-aged men.

Diagnosis: Early diagnosis is essential because this form of chronic hepatitis responds well to treatment. Other forms of hepatitis must be excluded, and the antibody tests covered above are done.

Confirm diagnosis by characteristic changes found on histologic examination of a **liver biopsy**. These changes are characteristic but not specific, so drug history and serologic tests are required to rule out other types of hepatitis.

Treatment: Unlike other types of hepatitis, patients with **autoimmune** chronic hepatitis usually have a **rapid reversal** of symptoms and increased survival with **prednisone +/- azathioprine**.

Azathioprine (AZA) is used as a steroid-sparing drug. Initially, AZA has no effect as a sole agent; although, over years, some patients can be tapered off steroids and remain on AZA.

Alpha-interferon (IFN- $\alpha$ ) **exacerbates** autoimmune hepatitis and is therefore **contraindicated** (although effective in chronic hepatitis B and C). So, it is vital to make the correct diagnosis.

Despite the usual response to treatment (above), there is **no cure** for autoimmune hepatitis, and it frequently progresses to cirrhosis and sometimes hepatocellular carcinoma (less often than with chronic viral hepatitis). Liver transplant is indicated for end-stage disease, although the disease process will slowly recur.

Table 1-13: DDx Chronic Hepatitis

|                      |                                                                                                                                                                                              |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A</b>             | Autoimmune may have <ul style="list-style-type: none"> <li>– ANA +/- anti-dsDNA</li> <li>– Anti-SMA</li> <li>– Anti-SLA antibody</li> <li>– Anti-actin antibody</li> <li>– p-ANCA</li> </ul> |
| <b>B</b>             | Hepatitis B                                                                                                                                                                                  |
| <b>C</b>             | Hepatitis C                                                                                                                                                                                  |
| <b>D<sub>1</sub></b> | Hepatitis D (only with Hep B)                                                                                                                                                                |
| <b>D<sub>2</sub></b> | Drugs (see text)                                                                                                                                                                             |
| <b>D<sub>3</sub></b> | Diseases: <ul style="list-style-type: none"> <li>– Wilson disease</li> <li>– <math>\alpha_1</math>-antitrypsin</li> <li>– Hemochromatosis</li> </ul>                                         |
| <b>F</b>             | NAFLD                                                                                                                                                                                        |

## Drug-Related Chronic Hepatitis

### Overview

Drug-related chronic hepatitis is associated with **methyldopa**, nitrofurantoin, acetaminophen, trazodone, phenytoin, methotrexate, oral contraceptives, and isoniazid (INH) (although **INH** far more commonly causes an **acute** hepatitis). Histologic changes are similar to autoimmune hepatitis, and the patients are often ANA+. Hypergammaglobulinemia is also often present. Best treatment is to stop the offending drug.

Drug-related liver disease (acute) can be caused by the direct **toxic**, **allergic**, and/or **idiosyncratic** effects of drugs. Acetaminophen causes a direct toxic effect. Drugs causing an idiosyncratic effect are: halothane, phenytoin, chlorpromazine, and erythromycin. Drugs causing **both** toxic and idiosyncratic effects: methyldopa, INH, and sodium valproate.

Birth control pills, anabolic steroids, chlorpromazine, and erythromycin are associated with cholestasis but **not** hepatitis.

Now let's talk a little more about acetaminophen, alcohol, methotrexate, INH, oral contraceptives, and aspirin.

### Acetaminophen

Acetaminophen poisoning is discussed under Poisoning in the General Internal Medicine section, Book 5. Briefly, when **acetaminophen** is ingested, 90% of it is processed via the glucuronidation pathway, 5% is excreted unchanged in the urine, and 5% is oxidized by the cytochrome P-450 system. The P-450 system produces a **toxic**, intermediate compound (N-acetyl-p-benzoquinoneimine, NAPQI), which is quickly reduced by glutathione. When there is an acetaminophen overdose, glutathione is rapidly depleted, and the resulting unreduced toxin causes direct liver damage.

Alcohol-acetaminophen syndrome: Chronic, moderate-to-heavy use of alcohol has a **2-fold** effect: the cytochrome P-450 system is cranked up (i.e., more NAPQI is produced) **and** the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-term users of moderate-to-heavy amounts of alcohol who take acetaminophen in **normal** or higher doses are at risk for **severe hepatic toxicity** or **liver failure**.

Glutathione levels are depressed in malnutrition. Acetaminophen liver toxicity also may develop by not eating for 3–4 days (e.g., with an acute viral illness) and taking **therapeutic** doses of acetaminophen; i.e., < 4 g/d!

30% of healthy people taking the maximum recommended dosage (4 grams per day) for 2 weeks will develop an ALT > 100 IU/L.

Again, [know]: Acetaminophen liver damage is potentiated with chronic alcohol use, one-time heavy alcohol use, malnutrition, chronic use, and even **dieting**.

Acetaminophen toxicity is the most common cause of **fulminant** hepatitis in the U.S. If suspected, draw acetaminophen blood levels; and treat early with intravenous or oral n-acetylcysteine (NAC; Mucomyst<sup>®</sup>, Mucosil<sup>®</sup>). The specifics of treatment are discussed under toxicities in the General Internal Medicine section, Book 5. There is also potential value to NAC treatment even with late diagnosis (more than 48 hours after ingestion and/or toxicity). Liver failure in this setting may be fatal or may require lifesaving liver transplant.

### Alcohol

Alcoholic liver disease results in a **macrovesicular** fat accumulation. There is also PMN infiltration in the liver. Women are more susceptible than men to alcoholic liver disease.

Alcohol induces GGT, so this enzyme is **disproportionately high** in alcoholic liver disease. Also, there is discordance between AST (SGOT) and ALT (SGPT) with an AST:ALT ratio of 3:1. The AST is virtually always < 300—even with severe alcoholic liver injury.

Direct toxic effect is modified by other factors—including nutrition. Toxic effects may be additive. Alcoholics are very susceptible to acetaminophen liver damage because alcohol induces the cytochrome P-450 system. The combination may cause fulminant hepatitis. Know that acetaminophen may not be given in the patient's history. Patients may know only that they have been taking a "non-prescription pain reliever."

Corticosteroids and pentoxifylline are of transient benefit in severe alcoholic hepatitis. Certain drugs cause a similar picture—see NAFLD, next page.

### Methotrexate

Methotrexate (MTX) can cause an indolent, asymptomatic liver disease that progresses to cirrhosis. Liver enzyme monitoring is recommended routinely in patients taking even intermittent doses of MTX.

### Isoniazid (INH)

INH causes an occasional, mild, transient increase in liver enzymes. 1% of these develop a more severe hepatitis—the frequency and severity of which correlate with **age**.

### Oral Contraceptives

Oral contraceptives (OCPs) are associated with benign, hepatic adenoma; peliosis hepatis (blood-filled sinusoids); and focal nodular hyperplasia of the liver. So, a young woman on OCPs who has a mass in her liver? Probably an **adenoma**. Hepatocellular cancer usually occurs in the setting of cirrhosis.

### Aspirin and Reye Syndrome

Reye syndrome occurs **exclusively** in children < 15 years old. Although rare, it tends to occur after a



## Quick Quiz

- What drugs are commonly associated with drug-induced hepatitis?
- How does alcohol intake affect liver toxicity from acetaminophen?
- What is nonalcoholic fatty liver disease (NAFLD), and who tends to get it?
- What are the treatment recommendations for NAFLD?
- What disease is most probable in a patient with tender hepatomegaly, a RUQ bruit, bloody ascites, a high alkaline phosphatase, and a very elevated alpha-fetoprotein level?

recent viral illness—especially influenza A or B or varicella (chicken pox)—and especially when there has been **concurrent ASA** use. These patients get a fatty liver (**microvesicular**—as in acute fatty liver of pregnancy) and progressive encephalopathy. Elevated are ALT, AST, NH<sub>3</sub>, and prothrombin time. Hypoglycemia, as a result of severe liver failure, is common. Mortality is 50%.

### Other Diseases that Cause Chronic Hepatitis

The main diseases besides hepatitis that cause chronic hepatitis are the following **hereditary** liver diseases. See Hereditary Liver Diseases on [page 1-59](#).

- Wilson disease
- $\alpha_1$ -antitrypsin deficiency
- Hemochromatosis

### NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Also called nonalcoholic steatohepatitis or NASH, NAFLD is an increasingly important cause of liver disease. NAFLD looks just like alcoholic liver disease, but there is **no** history of alcohol abuse. NAFLD is the inclusive term, which, like alcoholic liver disease, covers the spectrum of steatosis (fatty degeneration), steatohepatitis, fibrosis, and cirrhosis. 75–80% of **“cryptogenic”** cirrhosis is due to NAFLD.

The pattern of liver enzyme elevation is opposite that of alcoholic liver disease, with ALT > AST.

NAFLD is associated with the following:

- Obesity
- Type 2 DM
- Protein malnutrition
- Hyperlipidemia
- Amiodarone
- Corticosteroids
- “DROP”
- Prolonged IV
- Hyperalimentation

**DROP** is a metabolic syndrome with: Dyslipidemia, insulin Resistance, Obesity, and increased blood

Pressure. These patients with NAFLD and DROP have a higher incidence of **fibrosis**.

Treatment of NAFLD is **not** standardized. In general, treat with weight loss and control of any DM or hyperlipidemia. For patients with NAFLD and none of the common signs, recommend a low-fat diet. All patients with NAFLD should avoid alcohol.

### HEPATOCELLULAR CANCER

Hepatocellular cancer (HCC, hepatoma): 75% have antecedent cirrhosis. HCC is associated with **chronic liver disease** of **any** type: chronic hepatitis B and C, hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis. In addition, hepatomas are associated with **aflatoxin** exposure (can be found in raw peanuts or raw peanut butter, especially in Asia).

**Alcoholic** liver disease, frequently (75%) with **concurrent hepatitis C**, is the **most common** cause of HCC in the U.S. Chronic hepatitis B infection, acquired at birth, is the most common cause in developing countries.

HCC is associated with tender hepatomegaly, a **bruit** in RUQ, bloody ascites, and high alkaline phosphatase. 70–80% have a very elevated **alpha-fetoprotein (AFP)** level.

HCC-associated **paraneoplastic** syndromes are common and are clues to the diagnosis:

- Hypercalcemia (due to parathyroid-like hormone produced by the tumor)
- Hypoglycemia (due to tumor’s high metabolic needs or, more rarely, insulin-like growth factor II)
- Watery diarrhea
- FUO

Consider HCC in any cirrhotic who decompensates without an obvious reason. IFN- $\alpha$  treatment in **chronic hepatitis C** reduces the risk of HCC.

Screen all cirrhotics for HCC with abdominal **ultrasound** every 6 months. Alternately, some centers use **helical CT** or **MRI** which are more expensive, but either has **better** sensitivity than ultrasound.

Note yet again: Previously, alpha-fetoprotein test was also included as part of HCC screening, but the 2010 AASLD HCC Guideline notes that alpha-fetoprotein does **not** have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This guideline supports an ultrasound-alone strategy.

Know some basics about the treatment of liver cancer:

- 1) Resect a solitary tumor without vascular invasion (best  $\leq 5$  cm in diameter).
- 2) If unresectable or underlying liver disease is so bad (commonly due to cirrhosis), can consider for liver transplant.
- 3) Even with advanced disease, there are lots of options.

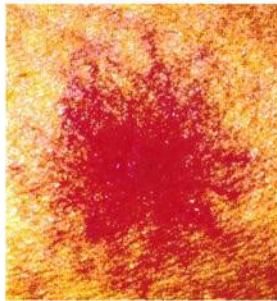


Image 1-23: Spider telangiectasia

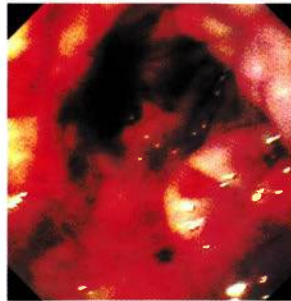


Image 1-24: Esophageal varices

## CIRRHOSIS

### Causes

- Alcohol (most common cause in U.S.)
- Hepatitis (B or C)
- Post-necrotic (drugs and toxins)
- Biliary disease
- $\alpha_1$ -antitrypsin deficiency
- Hemochromatosis
- Wilson disease
- Schistosomiasis
- Cardiac causes (primarily severe, prolonged right-sided CHF—which is rare)

### Stigmata of Cirrhosis

The physical exam findings of cirrhosis include any of the following alone or in combination(s):

- Hepatosplenomegaly
- Jaundice
- Ascites
- Caput medusae
- “Spiders” (telangiectasias) (Image 1-23)
- Gynecomastia and atrophy of the testicles in males
- Palmar erythema
- Fetus hepaticus
- Asterixis (in hepatic encephalopathy)
- Clubbing (usually in biliary causes)

### Complications of Cirrhosis

#### Esophageal Variceal Hemorrhage

##### Overview

1/3 of patients with esophageal varices bleed, and each bleed carries 1/3 mortality. With a bleed, the ratio of wedged:free portal pressure gradient is usually  $> 12$  mmHg (normal  $\leq 6$ ), but chance of bleeding better correlates with the **size** of the varices (Image 1-24).

##### Prophylaxis

Propranolol, with or without isosorbide dinitrate, decreases rebleeds and may delay or prevent the occurrence of the first variceal bleed. So propranolol is given

to **all** patients with large varices—whether or not they have had bleeding.

Sclerotherapy is **not** good prophylaxis against the first hemorrhage—it actually appears to make things worse.

What do you do for the patient with cirrhosis and small esophageal varices? Do nothing—only **big** varices bleed!

### Active Bleeds

Primary therapy of actively bleeding varices is **endoscopic banding or sclerotherapy**.

Somatostatin and its analog, octreotide, are splanchnic vasoconstrictors. These are frequently given parenterally in conjunction with endoscopic therapy and have a proven benefit over endoscopic therapy alone. Endoscopic injection of alcohol into bleeding varices temporarily stops the active bleeding, allowing for good visualization for banding or sclerotherapy.

Vasopressin, with simultaneous nitroglycerin (to minimize the vasoconstrictive side effect of vasopressin), has been used, but it is associated with more complications and is rarely used in the U.S.

Balloon tamponade is **rarely** used because it has a high rate of complications.

Any cirrhotic patient with GI bleeding should be carefully managed in the ICU. Consider elective airway intubation if there is active hematemesis because **aspiration pneumonia** is common. Always do endoscopy. Remember: Cirrhotics can bleed from sources **other** than varices; e.g., PUD. If the bleeding is due to varices, do endoscopic therapy with either banding or sclerotherapy.

Give all cirrhotic patients with bleeding varices or ascites prophylactic oral antibiotics to prevent spontaneous bacterial peritonitis (SBP).

### Preventing Rebleeds

Propranolol or other nonselective beta-blockers (nadolol) is given to **all** patients who have had bleeding varices to decrease the chance of rebleeds.

TIPS (transjugular intrahepatic portosystemic shunt) is used only for cases that **rebleed**. TIPS allows for decompression of the portal vein—effectively a portocaval shunt without the major surgery. The other main use for TIPS is for intractable ascites due to cirrhosis.

Summary of treatment for esophageal varices:

- Nothing for small varices
- **Propranolol** or **nadolol** for all large varices or any history of bleeding varices
- **Banding** or **sclerotherapy** for active bleeds or to prevent rebleeds—preferably with somatostatin
- **TIPS** for rebleeds



## Quick Quiz

- Name the causes of cirrhosis.
- Bleeding of esophageal varices is best correlated with what aspect of the varices?
- What drug is used for prophylaxis against bleeding with large esophageal varices? What do you do with small esophageal varices?
- What drugs and what endoscopic therapies are used for active variceal hemorrhages?
- What drug is given to a cirrhotic patient with a history of variceal hemorrhage to decrease the chance of rebleeds?
- If the PT is prolonged in an alcoholic and is easily corrected with vitamin K, what does this indicate?

### Hepatic Encephalopathy

Hepatic encephalopathy may be precipitated by:

- GI bleed
- Hypovolemia
- Increased dietary protein
- Hypoxia
- Hypokalemia
- Sedatives
- Tranquilizers
- Portal venous obstruction
- Infections (pneumonia, bacteremia, urosepsis, and spontaneous bacterial peritonitis—SBP)
- Alkalosis, which increases ammonia/ammonium ratio ( $\text{NH}_3/\text{NH}_4^+$ )—because only the non-ionized form,  $\text{NH}_3$  (ammonia), crosses the blood-brain barrier (Acidosis has the opposite effect.)

Signs of hepatic encephalopathy include fetor hepaticus (unique musty odor to breath and urine), hyperreflexia, asterixis, and altered mental status.

Treat with dietary **protein restriction** and **lactulose**. This disaccharide, more commonly used as an osmotic laxative, passes through the upper GI tract and is broken down by colonic bacteria into organic acids. The excess  $\text{H}^+$  in the proximal colon:

- inhibits coliform bacterial growth and thereby decreases  $\text{NH}_3$  production, and
- traps  $\text{NH}_3$  as inactive  $\text{NH}_4^+$ .

Supplemental/alternative treatments:

Oral antibiotics (also to decrease  $\text{NH}_3$  production) may be given if the patient doesn't respond to lactulose. Neomycin was previously used but has nephro/oto toxicity. Rifaximin, metronidazole, rifampin, and vancomycin are now used.

Acarbose (used for diabetes mellitus) inhibits breakdown of carbohydrates into monosaccharides. Monosaccharides promote the bacteria that produce ammonia.

Probiotics alter gut flora and similarly decrease ammonia levels.

### Hepatorenal Syndrome

Hepatorenal syndrome is also called “oliguric hepatic failure.” The renal failure is caused by renal vasoconstriction during severe, decompensated cirrhosis. Usually fatal. Frequently iatrogenic—secondary to diuretics, NSAIDs, aminoglycosides, IV contrast, and paracentesis, or may be due to GI bleed or sepsis.

Know: Urine sodium is very low in hepatorenal syndrome.

Current treatment: Careful volume management and midodrine (an  $\alpha_1$  agonist) + octreotide (stimulates fluid absorption from GI tract).

### PT in an Alcoholic

Again note: Alcohol causes **malabsorption** of some vitamins, including vitamin K. So, if the prothrombin time (PT) in an alcoholic is prolonged and is **easily corrected** by **IM** vitamin K, it is probably due to malabsorption—not liver disease, which affects more of the coagulation factors and is therefore harder to correct. Also, if a 1:1 mix corrects the PT, the disorder is due to decreased coagulation factors; if it does not correct, there is likely a circulating inhibitor.

## ASCITES

### Causes

Causes of ascites:

- Cirrhosis
- Alcoholic hepatitis
- CHF
- Constrictive pericarditis
- Peritoneal diseases
- Myxedema
- Nephrogenic ascites
- Chylous ascites
- Pseudochylous ascites
- Fulminant and subfulminant hepatitis
- Hepatic veno-occlusive disease (including Budd-Chiari)
- Hypoalbuminemia (nephritic syndrome, protein-losing enteropathy, severe malnutrition)
- Pancreatogenous (pseudocyst, disrupted duct)

Cirrhosis-induced ascites: Ascitic fluid is resorbed via the peritoneal surface. Maximum capacity is ~ 900 cc/d. So, if you try to diurese off > 1 liter/day, it is at the expense of intravascular volume. This disease causes the most avid sodium retention state known.

Note: A **chylous** ascites is due to lymphatic blockage (trauma, tumors—especially 1° lymphoma, TB, and filariasis), **not** cirrhosis or CHF.

### Diagnosis of Ascites

Determining the cause of ascites often requires analysis of a peritoneal fluid specimen for appearance, cell count with differential, cytology, total protein, and albumin.

Know all of the following:

**Appearance:** Bloody fluid suggests a tumor; cloudy, an infection; milky, lymphatic obstruction.

**Cell count:** If the cell count is elevated (> 250 PMNs), do a C&S and start antibiotics.

**Chemistry:** Portal hypertension is indicated by a serum-to-ascites albumin gradient (SAAG) > 1.1 g/dL. This occurs in ascites due to any of the following conditions (where albumin level in the ascites is low, usually < 1.0 g/dL):

- Cirrhosis (most common)
- RHF
- Fulminant liver failure
- Budd-Chiari syndrome
- Myxedema

A SAAG < 1.1 g/dL (i.e., high level of albumin in the ascites and **no** portal HTN) is seen with ascites due to tuberculosis peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis. Note: SAAG is a difference, not a ratio! It is defined by:

$$\text{SAAG} = \text{Albumin}_{\text{Serum}} - \text{Albumin}_{\text{Ascites}}$$

An elevated ascites **protein** level ( $\geq 2.5$ ) is seen in all cases that cause increased levels of albumin. It is **also** seen in **cardiac** ascites! See Table 1-14.

TIPS (transjugular intrahepatic portosystemic shunt) is used to treat ascites caused by cirrhosis. As stated before, TIPS allows for decompression of the portal vein—effectively a portocaval shunt without the major

surgery. A common complication of TIPS is **encephalopathy**; therefore, it is generally not recommended for elderly patients—who are most susceptible. As previously discussed, TIPS is also used in the treatment of rebleeding esophageal varices.

### Spontaneous Bacterial Peritonitis (SBP)

Spontaneous bacterial peritonitis (**SBP**) is indicated by a peritoneal fluid with > 250 PMN/mL in a patient with ascites. Usual causes are *E. coli*, then *S. pneumoniae*, then *Klebsiella*.

Because SBP patients may not have abdominal pain or tenderness, you must consider SBP if there is deterioration in the status of any patient with ascites; e.g., new-onset confusion, fever, signs of hepatic encephalopathy, or renal failure.

Risk factors for SBP:

- Ascites protein < 1.0 g/dL
- History of variceal bleed
- Prior episode of SBP

Patients with these risk factors should receive either **intermittent** (preferred) or continuous **prophylactic** oral antibiotic therapy. Typically use oral therapy with a quinolone or TMP/SMX.

You must rule out 2 other possible causes of high WBC in ascitic fluid before you can assume it is SBP:

- 1) Neutrocytic ascites: Basically, this is PMNs > 250/mL with **no** evidence of **SBP** and negative cultures.
- 2) Primary bacterial peritonitis (**PBP**) is due to perforated viscus. In cirrhotics, it can be confused with SBP.

Note that **PBP** has markedly different ascitic fluid lab findings than SBP:

- Protein > 1 g/dL, frequently > 3 g/dL
- Glucose < 50 g/dL
- WBC very elevated, often > 5,000
- Ascites fluid LDH > serum LDH

Treatment: Active SBP is usually treated with cefotaxime (Claforan®) or similar spectrum 3<sup>rd</sup> generation cephalosporin. Milder cases can be treated with oral antibiotics.

IV **albumin** is also given in the treatment of SBP. Albumin maintains blood volume and thereby decreases the incidence of irreversible renal impairment and mortality.

### Treatment of Ascites

Treatment: mainly dietary sodium and water restriction (needed only if the  $\text{Na}^+ < 125$ ). Then, if needed, start spironolactone, then a loop diuretic. Stop all anti-prostaglandin medications (e.g., ASA) because these decrease

**Table 1-14: Causes of Ascites and Associated Findings**

| Protein and Albumin in Ascites                                                                                |                                |                       |
|---------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------|
| Causes                                                                                                        | (Serum) -<br>(Ascites) Albumin | Ascites<br>T. protein |
| Cirrhosis, liver failure, Budd-Chiari syndrome, myxedema, and SBP                                             | > 1.1                          | < 2.5                 |
| Right heart failure                                                                                           | > 1.1                          | > 2.5                 |
| TB peritonitis, bacterial/fungal peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis | < 1.1                          | > 2.5                 |



## Quick Quiz

- What is chylous ascites due to?
- How does SBP differ from neutrocytic ascites?
- How does SBP differ from PBP?
- Why is albumin given in the treatment of SBP?
- What hereditary liver disease has increased unconjugated bilirubin?
- When does jaundice in Gilbert syndrome typically occur?

urinary  $\text{Na}^+$  excretion! Also, do not give an aminoglycoside in this setting because it may precipitate renal failure.

Again, do **not** diurese  $> 1$  liter/d. It is okay to do daily paracenteses (up to 4 liters/d) during the **initial treatment** of recent-onset ascites or with severe **refractory** ascites **if** the patient's renal function is normal and there is:

- **No** GI bleeding
- **No** sepsis
- **No** portosystemic encephalopathy (PSE)

With large-volume paracentesis, replace 8 grams albumin for each liter of fluid removed. Also, give albumin IV in life-threatening ascites, **although** it has only a short-term effect.

## HEREDITARY LIVER DISEASE

### Review of Bilirubin

Hyperbilirubinemia is the main finding in hereditary liver diseases.

In general, only **conjugated** bilirubin passes the glomeruli and is excreted in the urine. The unconjugated bilirubin is tightly bound to albumin, and this complex is too large to pass through the glomerulus. Conjugated bilirubin is less tightly bound to albumin, and the 5% unbound portion easily passes into the urine.

So—**bilirubinuria** results only from **conjugated** hyperbilirubinemia. Because bilirubin is conjugated in the liver, bilirubinuria is an indication of cholestasis.

### Unconjugated Bilirubin

Gilbert syndrome is a very common, benign, chronic disorder resulting in a mild, **unconjugated** hyperbilirubinemia. **Remember: unconjugated = indirect = without bilirubinuria.** Jaundice may come and go and is typically brought on by physical stress (especially surgery, exertion, and infection), fasting, and alcohol ingestion. Around 7% of the population has Gilbert syndrome. It appears to be an **autosomal dominant** syndrome with variable penetrance.

Gilbert syndrome is due to decreased or absent glucuronyl transferase in the liver cells or decreased liver cell uptake of unconjugated bilirubin. 1/2 of patients have a very low-grade, chronic hemolysis. This probably reflects 2 separate syndromes, but, for now, they are still grouped together. Phenobarbital stimulates glucuronyl transferase and decreases the bilirubin level.

Diagnosis: Increased unconjugated bilirubin after prolonged fasting. **No** treatment is needed.

### Conjugated Bilirubin

If a patient is noted to have increased **conjugated** bilirubin after a major surgery, it is **not** Gilbert syndrome (which is **unconjugated**). It is most likely an entity called **benign postoperative cholestasis**. This is most often seen if the patient became hypotensive or required many transfusions during the operation.

### $\alpha_1$ -Antitrypsin Deficiency

$\alpha_1$ -antitrypsin deficiency (autosomal recessive) mainly affects the liver and lungs and causes a chronic hepatitis that eventually leads to cirrhosis and emphysema. Diagnose with electrophoresis.

Treatment: Other than liver transplant or liver + lung transplant, the only other minimally effective treatment is augmentation therapy with weekly infusions of pooled human AAT ( $\alpha_1$ -antiprotease).

### Hemochromatosis

Know this topic. Consider all the following highlighted!

Two types of hemochromatosis: **genetic** and **acquired**.

The genetic form involves the **HFE** gene and is autosomal recessive (AR).

The **acquired** form is usually from multiple blood transfusions because of underlying anemia, such as sickle cell disease, or less frequently due to an iron-loading chronic anemia with 2° erythropoiesis, such as **sideroblastic** anemia or **thalassemia**. This form usually develops in men between ages 40 and 60 years.

In **both** genetic and acquired types, there is abnormally increased intestinal iron absorption, which leads to iron deposition in the tissues. This iron deposition causes fibrosis and damage to organs—especially the **liver, heart, pancreas, and pituitary**.

Note: Symptomatic hemochromatosis is 10x more frequent in men—this is probably because of the effect menses has on iron stores in women.

Clinical findings:

- Hepatomegaly (95%)
- Gray hyperpigmentation (90%)
- Secondary diabetes (65%), so suspect this in a 50-year-old with new-onset DM

- Arthropathy (40%—especially 2<sup>nd</sup> and 3<sup>rd</sup> MCP joints of the wrist!)
- Cardiac involvement (15%)

Secondary hypogonadism also occurs and is caused by depression of the hypothalamic-pituitary axis. There is a 25–30% risk for **hepatocellular cancer** in patients with cirrhosis caused by hemochromatosis—higher than any other cause!

Diagnosis of hemochromatosis is **suggested** by high levels of serum **Fe**, **ferritin**, and **transferrin** levels. The most helpful screening test is **transferrin saturation > 45%**. (You can read up on these lab tests at the beginning of the Hematology section, Book 4.) Liver biopsy **confirms** the diagnosis and allows for staging of fibrosis.

Liver biopsy is indicated for serum ferritin > 1,000 ng/mL.

Confirm the diagnosis for the hereditary type with an assay for the **HFE** gene.

If this disease is successfully treated early enough—especially if prior to development of cirrhosis—patients have a normal life span with negligible risk of cancer. Initial treatment is weekly **phlebotomy**. Ultimately, the patient has phlebotomy 4x/year with the goal of a **ferritin** level between **50** and **100** ng/mL. This treatment results in decreased skin pigmentation, improved cardiac function, and prolonged life expectancy. But, if already lost, the secondary sex characteristics do not return; the damage is done!

### Wilson Disease

Wilson disease is an AR disorder that usually presents as liver disease **or** neurologic/psychiatric dysfunction in **adolescents**. It usually presents between ages 15 and 25. Other symptoms include arthritis from chondrocalcinosis. Wilson disease is caused by impaired excretion of copper into bile, which results in an excess copper in body tissues—especially the liver.

Hemolysis is common. Serum ceruloplasmin is **low** (in most liver diseases, it is high) and **urinary** copper level is **high**. Kayser-Fleischer rings are pathognomonic: a single brownish corneal ring in each eye, formed by copper deposition along the outer edge of the **cornea** (Image 1-25). Liver biopsy **confirms** the diagnosis; it shows a high liver copper level—but remember, so do PBC and PSC!

Screen with the following tests for Wilson disease in all adults with chronic liver disease without obvious cause, especially if younger than 40 years of age:

- Serum ceruloplasmin
- Slit lamp exam
- Urine copper

All 3 of the above are positive in < 50% of patients with Wilson disease.

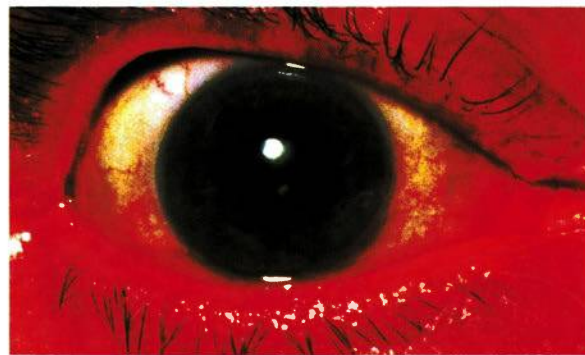


Image 1-25: Kayser-Fleischer ring on rim of iris of the eye

Treatment of Wilson disease is a **2-phase** process. First, decrease copper levels, usually with chelation. Then, order maintenance therapy to prevent reaccumulation of copper.

**Phase 1:** Chelation with **penicillamine** (must give supplemental pyridoxine with this drug). If the patient cannot tolerate penicillamine or has progressive neurologic manifestations, use trientine. Zinc is a 3<sup>rd</sup> option.

**Phase 2:** Maintenance therapy with low-dose penicillamine or trientine, or with zinc. Oral zinc blocks the absorption of copper. Low-copper diet is **required** (avoid nuts, peas, chocolate, mushrooms, shellfish, liver).

A liver transplant **cures** Wilson disease!

In **fulminant** Wilson disease, there is severe hemolytic anemia and a high serum copper level due to the release of copper from the liver. Penicillamine therapy is not effective; the only treatment is liver transplant.

### LIVER DISEASE DURING PREGNANCY

#### 1<sup>st</sup> Trimester

- Hyperemesis gravidarum can cause N/V, volume depletion, and mild increase in AST and ALT.

#### 2<sup>nd</sup> Trimester

- 2<sup>nd</sup> trimester is the best time for surgery for severely symptomatic gallstone patients.

#### 3<sup>rd</sup> Trimester

- Remember that **hepatitis E** can cause fulminant hepatitis in the 3<sup>rd</sup> trimester of pregnancy—with a 20% fatality rate.
- Fatty liver of pregnancy is a very serious condition in which there is **microvesicular** fat deposition in the liver (as in Reye syndrome), with only modest elevation of AST/ALT/Bili. It occurs in the 3<sup>rd</sup> trimester and is associated with encephalopathy, hypoglycemia (again like Reye syndrome), preeclampsia, pancreatitis, DIC, and renal failure. Early delivery is required.
- **HELLP** syndrome: **H**emolysis, **E**levated **L**iver **E**nzymes, **L**ow **P**latelets. Most patients also have



## Quick Quiz

- What is the risk of hepatocellular cancer in a patient with cirrhosis caused by hemochromatosis?
- What lab findings are common in Wilson disease?
- What is a pathognomonic finding in Wilson disease?
- Which patients should be considered for a liver transplant?
- What is the usual cause of jaundice in persons < 30 years old? 40–60? 60–80?

hypertension and proteinuria. This is thought by most to be a **severe variant of preeclampsia** that occurs before 36 weeks of pregnancy. Delivery of the infant is the only consistently beneficial treatment.

- Intrahepatic cholestasis of pregnancy causes **itching** and increased alk phos, bili, AST, and ALT.

## LIVER TRANSPLANT

[Know!] Consider liver transplant for **almost all** patients with irreversible end-stage acute and chronic liver disease. The selection process excludes many of these patients. The selection is usually made by a liver transplant committee at the liver transplant center. The process is inexact, and the waiting period for a liver is often more than a year. Evaluate patients with chronic, progressive liver disease early in the course of the disease.

The Model for End-stage Liver Disease (MELD) scale gives a fairly accurate short-term (3–6 month) prediction of **mortality** risk, and it is used to determine organ allocation for liver transplant. It uses bilirubin and creatinine levels, INR (normalized prothrombin time), and etiology of liver disease in its calculation. The MELD score:

$$3.8 \log_e (\text{bilirubin [mg/dL]}) + 11.2 \log_e (\text{INR}) + 9.6 \log_e (\text{creatinine [mg/dL]}) + 6.4 (\text{etiology})$$

“etiology” = 0 if cholestatic or alcoholic, 1 otherwise.

Be sure and know this formula for the exam! And know the quick way to do logs without a calculator. (Just kidding ... on both counts.) Actually, all you might need to know about the MELD score is:

- < 10 = won't be on the transplant list unless patient has a liver tumor
- > 20 = candidate for transplant

Common indications for liver transplant: **Most** types of chronic end-stage liver disease, metabolic liver disease, primary and secondary biliary cirrhosis, primary

sclerosing cholangitis, and fulminant hepatitis. Cirrhosis with a small, early-stage hepatocellular cancer (HCC) is another indication.

Associated biochemical indications seen in end-stage chronic liver disease: bilirubin 10–15 mg/dL, albumin < 2.5, and a PT > 3–5 sec above normal (10–12 sec). Other signs/symptoms suggesting it is time to transplant: intractable pruritus, hepatic encephalopathy, bacterial peritonitis, intractable ascites, and the development of hepatocellular carcinoma.

Controversial: liver transplant to treat alcoholic cirrhosis.

**Absolute** contraindications: preexisting advanced or uncontrolled nonhepatic disease, active alcohol or drug abuse, life-threatening systemic disease, and metastatic cancer. There are many relative contraindications, including advanced age.

A prior TIPS (see [page 1-56](#) under Complications of Cirrhosis) is **not** a contraindication to transplant. In fact, it is often a lifesaving “bridge” to transplantation.

## JAUNDICE

We've discussed many of the causes of jaundice in this section, and now we'll summarize these with a quick review of the workup of a patient with jaundice.

The differential diagnoses of jaundice include:

- |                                |                                   |
|--------------------------------|-----------------------------------|
| • Viral hepatitis              | • Sickle cell disease             |
| • Drug-induced jaundice        | • Gilbert syndrome                |
| • Alcoholic liver disease      | • Primary biliary cirrhosis (PBC) |
| • Chronic hepatitis            | • Ascariasis                      |
| • Gallstones and complications | • Primary sclerosing cholangitis  |
| • Pancreatic cancer            |                                   |

... **but** the majority fall into the following 3 causes:

- 1) Acute viral hepatitis
- 2) Chronic cirrhosis
- 3) Obstructive problem (common duct stone or pancreatic cancer)

And these 3 causes are strongly associated with certain age groups:

- 1) Acute viral hepatitis is the most common cause (**85–90%**) in those **< 30** years old.
- 2) Chronic cirrhosis is the usual cause (**50–70%**) in those **40–60** years old.
- 3) Obstructive jaundice (common duct stone or pancreatic cancer) is the usual cause (**80%**) in those **60–80** years old without other risk factors.

If the patient is recently from outside the U.S., consider ascariasis—especially if that patient has eosinophilia.

**Table 1-15:** Workup of Jaundice

|                                              | <b>Acute<br/>Viral<br/>Hepati-<br/>tis</b> | <b>Chronic<br/>Cirrhosis</b>                 | <b>Obstructive:<br/>CD Stone or<br/>Pancreatic<br/>Cancer</b> |
|----------------------------------------------|--------------------------------------------|----------------------------------------------|---------------------------------------------------------------|
| <b>Bilirubin</b>                             | < 20                                       | < 20 unless<br>impaired<br>renal<br>function | < 20                                                          |
| <b>ALT/AST</b>                               | > 400                                      | < 400                                        | < 400 usually                                                 |
| <b>Alk Phos</b>                              | NL–<br>2xULN                               | NL–4xULN                                     | 4–10xULN                                                      |
| <b>A/G</b>                                   | NL/NL                                      | Low/High                                     | Usually NL/NL                                                 |
| <b>PT/PTT</b>                                | NL/NL<br>usu                               | High/High                                    | Usually NL/NL                                                 |
| <b>Cholesterol</b>                           | NL                                         | NL to Low                                    | NL to High                                                    |
| <b>Serologies<br/>A,B,C<br/>EBV,<br/>CMV</b> | May be<br>helpful                          | Excludes<br>acute<br>viral etio if<br>needed | Excludes acute<br>viral etio if<br>needed                     |
| <b>Abd U/S</b>                               | NL                                         | May be<br>helpful                            | 93/95 Sens&Spec<br>if bili > 10 x 10 d                        |

Jaundice workup consists of:

- a careful history,
- ultrasound, and
- LFTs (Table 1-15).

Ultrasound results determine the next test to be done:

- Dilated common bile duct **and stones**: ERCP
- Dilated common bile duct and **no stones**: CT (Think pancreatic cancer.)
- Dilated intrahepatic ducts: CT
- Dilated ducts and testing to exclude PSC: MRCP
- If **no** dilated ducts: liver **biopsy**

## NUTRITION

### VITAMIN DEFICIENCIES

#### Time Until Onset of Symptoms

[Know!] The time until onset of symptoms of vitamin or mineral deficiency—as when on TPN without vitamin supplementation (and barring other problems):

**Weeks:** **water-soluble vitamins**, **magnesium** (muscle stiffness and cramps—often causes tetany in patients with Crohn disease), **zinc** (acrodermatitis and poor wound healing), and **essential fatty acids**

**Months:** **Cu** (hypochromic, microcytic anemia) and **vitamin K** (bleeding, high PT)

**Year:** **vitamins A and D**, **selenium** (myalgias, cardiomyopathy, and hemolytic anemia), and **chromium** (glucose intolerance and peripheral neuropathy)

**Several years:** **iron**, **cobalt** (anemia)

**Many years:** **B<sub>12</sub>**

These deficiencies are important. [Know them cold!] A good way to review this section is to fill in the following sentence, using the appropriate times, symptoms, and mineral deficiencies from above.

If, after 1–2 (\_\_\_\_), a patient on TPN develops (\_\_\_\_), you would suspect (\_\_\_\_).

More on vitamin deficiencies: Vitamins B and C are water-soluble, while vitamins A, D, E, and K are lipid-soluble. These will be discussed in this order. [Know **all** this info about vitamins and minerals!]

#### Vitamin A Deficiency

Vitamin A deficiency is a major cause of blindness in developing countries; night blindness is the earliest symptom of deficiency.

#### Vitamin B<sub>1</sub> Deficiency

Vitamin B<sub>1</sub> is thiamine. Thiamine deficiency causes **beriberi**. It usually develops in alcoholics or in patients on chronic dialysis. There are 2 major manifestations of thiamine deficiency: wet beriberi and dry beriberi.

- **Wet beriberi:** Symptoms of wet beriberi are heart failure, ascites, and often an accompanying peripheral edema.
- **Dry beriberi** is confined to the nervous system:
  - peripheral neuropathy (symmetrical sensory, motor, and reflex loss),
  - **Wernicke** encephalopathy (vomiting and nystagmus, ophthalmoplegia, ataxia, and mental deterioration), and
  - **Korsakoff** syndrome (confabulation, poor recent memory and learning).

Thiamine replacement usually cures Wernicke encephalopathy, but it reverses symptoms in only 1/2 of patients with Korsakoff syndrome—and fully cures only 25%.

Glucose infusions may precipitate Wernicke encephalopathy, so a classic presentation is a closet drinker who develops **ophthalmoplegia or nystagmus post-surgery**. **Always** give thiamine to an alcoholic **before** starting an IV **glucose** solution.

Wernicke encephalopathy is a medical emergency. Immediately give thiamine 50 mg IM or IV. Repeat daily until the patient is able to take it orally.

#### Vitamin B<sub>2</sub> Deficiency

Vitamin B<sub>2</sub> is riboflavin. B<sub>2</sub> deficiency almost invariably occurs in association with other vitamin deficiencies. **Phenothiazines** and **tricyclic antidepressants** increase the tendency to develop riboflavin deficiency. Patients present with a normochromic normocytic anemia, sore throat with hyperemic mucosa and glossitis, cheilosis,



## Quick Quiz

- What is the timeframe for development of vitamin deficiency for each of these:  
a) water-soluble vitamins, b) vitamin A and D, c) iron and cobalt, d) B<sub>12</sub>?
- What are the symptoms of wet beriberi? Dry beriberi?
- What is the classic presentation of a patient with Wernicke encephalopathy?
- Petechiae are associated with which vitamin deficiency?
- Explain how vitamin D is produced and altered in the body.
- What does vitamin D deficiency cause in the adult?
- What are the findings associated with excessive continuous ingestion of vitamin B<sub>6</sub>?

angular stomatitis, and a seborrheic dermatitis, especially involving the perineal/scrotal area. Symptoms are reversed with riboflavin.

### Vitamin B<sub>6</sub> Deficiency

Vitamin B<sub>6</sub> is pyridoxine. Deficiency is rare and usually caused by drugs but may also be seen with general malabsorption syndromes and chronic alcoholism. The main drug culprits are INH, cycloserine, and penicillamine. Presenting symptoms include glossitis, cheilosis, vomiting, and **seizures**.

### Vitamin B<sub>12</sub> Deficiency

Vitamin B<sub>12</sub> deficiency is discussed in the Hematology section, Book 4, under Nuclear Maturation Defects, and the Neurology section, Book 5, under Myelopathies. It results in a **macrocytic** anemia; smooth tongue; and subacute, combined degeneration of the spinal cord, causing initial pins-and-needles feeling, then decreased vibration and proprioception (position) sense and a **stocking/glove** decreased reaction to **pinprick**; and dementia.

### Niacin Deficiency

Niacin deficiency causes **pellagra**. Niacin (nicotinic acid) is made from tryptophan in the body (so it is not actually a “vitamin”). Niacin deficiency is rare in the U.S. because niacin is now added to grains. It is still seen in **carcinoid** syndrome, in which tryptophan is used up, and when isoniazid (INH) is used in treating TB. Presenting signs of niacin deficiency are a **dermatitis**—especially on sun-exposed surfaces, glossitis (“bald tongue”), stomatitis, proctitis, diarrhea, and changing mental status—ranging from depression to dementia

to psychosis. (Remember these by the 3 Ds: mucosal Dermatitis, Diarrhea, and Dementia.) Patients may be hyperpigmented.

### Vitamin C Deficiency

Vitamin C (ascorbic acid) deficiency causes **scurvy**. Ascorbic acid is a vital vitamin in connective tissue formation. Scurvy usually occurs in poverty-stricken urban areas. First symptoms are **petechial** hemorrhages and **ecchymoses**; then the patient gets hyperkeratotic papules around hair follicles, Sjögren syndrome, hemorrhage into muscles and joints, purpura, and splinter hemorrhages in the nail beds. In children, it affects bone formation and can cause intracerebral hemorrhage. Symptoms improve only when the normal pool is replenished (1.5–3 grams).

### Vitamin D Deficiency

Vitamin D deficiency causes rickets in children and osteomalacia in adults. Most vitamin D is synthesized in the skin (from a provitamin D + sunlight), but some is absorbed from the gut. This vitamin D is then converted to 25-OH-D in the liver and further to 1,25-(OH)<sub>2</sub>-D in the kidney—the active form of vitamin D.

25-OH-D is what is usually measured on blood tests. 1,25-(OH)<sub>2</sub>-D levels are quite labile and are not routinely be measured due to poor reproducibility.

Vitamin D deficiency causes decreased absorption of calcium from the gut and decreased calcium resorption from the kidney. Deficiency also stimulates the release of PTH. Early in the course of the disease, the hypocalcemia is blunted by the increase in PTH, which increases absorption from the gut and also leaches calcium from the bones; so even though there is normal or slightly low serum calcium, the patient still gets the bone problems!

Symptoms in adults are often just musculoskeletal pain and weakness.

Main causes of decreased vitamin 1,25-(OH)<sub>2</sub>-D:

- Decreased production in skin
- Elderly: decreased skin synthesis at age > 70
- Winter: decreased sun exposure (Roughly 40% in northern climes are deficient at end of winter.)
- Decreased intestinal absorption: steatorrhea, insufficient dietary intake
- Kidney disease

Consider vitamin D deficiency especially in any older patient who has musculoskeletal pain/weakness and especially if there is a history of fat **malabsorption** or the patient does **not eat meat**. If osteopenia is diagnosed, check 25-OH-D levels.

### Vitamin E Deficiency

Vitamin E is an antioxidant. Deficiency is rare and is usually seen when there is fat malabsorption and also a deficiency of the other fat-soluble vitamins. Deficient patients can have areflexia and decreased vibration and position sense.

## VITAMIN OVERDOSE

### Vitamin A

Hypervitaminosis A can be caused by eating polar bear liver, but it is more commonly a result of over-ingestion of vitamin supplements, causing headache and flaky skin. A single massive dose causes abdominal pain, sluggishness, papilledema, and a bulging fontanel in infants. This is followed in a few days with desquamation of the skin and recovery. Chronic over-ingestion (25,000 IU/d) is associated with arthralgias, anorexia, dry skin, hair loss, low-grade fever, and hepatosplenomegaly.

### Vitamin B<sub>6</sub>

Vitamin B<sub>6</sub> excess can cause a peripheral neuropathy with normal motor and sensory function, but absent positional and vibratory sensation.

### Vitamin D

Hypervitaminosis D results in increased calcium absorption from the bowel, hypercalcemia, and hypercalciuria. It probably increases the tendency for calcium renal stones. The hypercalcemia and hypercalciuria seen in chronic granulomatous diseases (such as sarcoidosis and lymphomas) are due to an equivalent hypervitaminosis D state, in which there is increased 1,25-(OH)<sub>2</sub>-D.

### Vitamin E

Vitamin E is relatively nontoxic acutely. The main trouble with vitamin E is that large doses can cause a marked **potentiation of oral anticoagulants**. Long-term vitamin E supplementation has been associated with increased all-cause mortality.

### Vitamin C

Vitamin C megadoses increase the possibility of **oxalate** renal stones and can interfere with the absorption of B<sub>12</sub>.

### Niacin

High doses of niacin can cause acanthosis nigricans and cholestatic jaundice. The flushing and pruritus often occurring at the start of treatment are prevented by taking aspirin 30 minutes before the niacin and/or by taking niacin in divided doses or after meals.

## ENTERIC FEEDING vs. TPN

If the choice is between enteric feeding and TPN, enteric feeding is the better option. The glutamine and short-chained fatty acid substrates (fatty acids are manufactured in the small intestine) in the enteric feedings help **maintain the integrity of the small intestinal wall**—the loss of which is associated with the onset of multisystem failure. Glutamine is too unstable to be used in TPN. Percutaneous endoscopic gastrostomy is often used in patients who cannot swallow. It is a better alternative to the NG tube, and general anesthesia is not required. Contraindications to percutaneous endoscopic gastrostomy are delayed gastric emptying and gastric outlet obstruction. In these cases, various types of jejunostomy tubes can be used.

## MALNUTRITION

Simple clues to malnutrition:

- Weight/ideal weight < 70%
- Lymphocyte count < 1,000/mm<sup>3</sup>
- Low albumin or **prealbumin**
- Low triceps skin-fold thickness
- Low urine creatinine-to-height ratio = (24-hr urine excretion of creatinine in µg) ÷ (height in centimeters) < 10 in men, < 6 in women.

Greater than 10% **weight loss** over 6 months indicates a possibility of malnutrition. **Albumin** is an indicator of nutritional status, but it may also be lower after major trauma or during an infection (due to vascular leakage of albumin or decreased albumin production by the liver). Malnourished patients are typically **anergic**. **Triceps skin-fold** measurement is good only for **long-term** assessment of nutritional status. Short-term changes may not be meaningful because of changes in hydration and edema.

Indirect calorimetry units that measure oxygen consumption and CO<sub>2</sub> production are more precise and usually better for determining needed calories for in-hospital, critically ill patients.

Refeeding syndrome: Chronically malnourished patients (e.g., anorexia nervosa, cancer, short gut)—especially those with resting bradycardia, hypotension, or body weight < 80% ideal weight—are **at risk for cardiac failure with rapid refeeding**. Phosphate replacement, frequent monitoring of electrolytes, and cardiac telemetry should be used during the initial days of refeeding to minimize the risk for cardiac failure.



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INFECTIOUS DISEASE

# INFECTIOUS DISEASE

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## HOST DEFENSE

## CYTOKINES

See the Allergy & Immunology section, Book 4, for a description of the basic functions of the immune system.

Cytokines are signaling molecules produced by immune system cells. These molecules facilitate communication among branches of the immune system. After release, they bind target receptors on other immune system cells to result in an alteration in cell function. The molecules can ramp up the immune system or tone it down.

Examples of cytokine types include colony-stimulating factors (CSFs), interferons (IFNs), interleukins (ILs), and growth factors (Table 2-1).

Cytokine releases and responses are extensive topics. Covered here are the most clinically relevant interactions and cytokines. Among T cells, cytokines are released in response to an interaction between the **T cell**, an **antigen-presenting cell**, and the **antigen**. The cytokines produced depend on the type of T cell involved (termed a “T-cell subset”) and the cytokine profile of that subset.

Major subsets include **T-helper** (Th) 0, Th1, Th2, and Th17:

- **Th0** cells are unrestricted. They are naïve T cells that can respond to novel antigens that the immune system has not yet encountered.
- **Th1** cells produce IFN-gamma, IL-2; are important in **cell-mediated** immune response (e.g., delayed-type hypersensitivity reaction); and are stimulated by the IL-12 superfamily.
- **Th2** cells produce IL-4, IL-10; are important in **humoral** immune response (antibody development and allergic responses); and are stimulated by IL-4, -33, -18 working together.
- **Th17** cells produce IL-17A, -17F, -22; are important in **antifungal immunity** and also **autoimmune-related** chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory myopathies); and are stimulated by IL-1, -6, -21, -23.

Cytokines that mediate **cellular migration** into tissue are called chemokines. IL-8 is an example.

Some cytokines that **inhibit** the immune system are prostaglandins, transforming growth factor (TGF)-beta, and IL-10.

Many believe that unregulated cytokine activation is the origin of systemic inflammatory response syndrome (SIRS), which is a severe condition with systemic inflammation and organ dysfunction and failure. SIRS may have an infectious or a noninfectious etiology. When **infection** is suspected or demonstrated, the condition is called **sepsis**. Tumor necrosis factor (TNF)-α may be the most important mediator. TNF-α is a cytokine released by neutrophils, monocytes, and macrophages in response to endotoxin (lipopolysaccharide; LPS). Once released, TNF-α amplifies the signal LPS and transmits it to other cells.

Table 2-1: Cytokines

| Type                           | Functions                                                                        |
|--------------------------------|----------------------------------------------------------------------------------|
| <b>Interleukins</b>            |                                                                                  |
| IL-1                           | Fever, stimulates T cells                                                        |
| IL-2                           | Proliferates T cells, activates B cells                                          |
| IL-4                           | Immunoglobulin switch signal, suppresses Th1                                     |
| IL-6                           | Cell proliferator, acute-phase reactant                                          |
| IL-12                          | Increases IFN-gamma, induces Th1 differentiation                                 |
| IL-15                          | Induces TNF-alpha release                                                        |
| IL-17                          | Important in autoimmune chronic inflammatory reactions and anti-fungal immunity. |
| TNF-alpha                      | Cachexia, stimulates T cell                                                      |
| IFN-gamma                      | Activates T cells, NK cells, macrophages                                         |
| TGF-beta                       | Inhibits T-cell proliferation and pro-inflammatory cytokines                     |
| Platelet-derived growth factor | Proliferates fibroblasts                                                         |

## NEUTROPENIA

## Epidemiology and Risk Factors

Neutropenia (granulocytopenia) occurs in leukemia, bone marrow transplant, ablative chemotherapy, metastases to the bone marrow, and overwhelming sepsis. Previously, the most common bacterial infections in patients with neutropenia were caused by gram-negative organisms, but this has shifted to **gram positives**—probably due to the widespread use of 3<sup>rd</sup> generation cephalosporins and to increased central venous catheter use. Most often, the infections are caused by flora that are colonizing the patient and that enter the bloodstream across disrupted gut mucosa, via an intravenous catheter, or through the oropharynx into the lungs and/or sinuses.

Of the gram positives, the most common are *S. aureus*, *S. epidermidis*, and the streptococci. But we are now seeing more infections associated with the less common gram-positive organisms such as *Corynebacterium*, *P. acnes*, *Bacillus*, and *Leuconostoc*. These are important to remember because some are **not** effectively treated with **vancomycin**.

Gram-negative infections are still common, especially *Pseudomonas* and the other drug-resistant gram-negative rods (GNRs).

Anaerobic infections are **not** seen commonly in neutropenia.

Fungi, especially the candidal yeasts that colonize the gut mucosa, are very important pathogens. Molds such

as *Aspergillus*, however, are also major causes of disease in neutropenics. Know that infections with *Fusarium* are especially **deadly** and are being seen more frequently. Fungi are not equally susceptible to antifungal drugs. When a patient with neutropenia develops fever and/or an infection while receiving an empiric antifungal drug, it is very important to know which organisms are resistant to that antifungal (and possibly the cause).

The tendency for infection in the patient with neutropenia is directly proportional to the reduction in granulocytes below **500 cells/mm<sup>3</sup>**. Other relevant factors:

- Rapidity and duration of neutropenia (rapid and longer duration = increased risk of fungal infections)
- Comorbid diseases
- Presence of catheters
- Drugs given to treat the disease that causes the neutropenia, especially monoclonal antibodies and corticosteroids (risk of *Pneumocystis* and tuberculosis)

The absolute number of granulocytes is definitely important; however, patients can actually have an adequate number of cells yet still get infected if the present granulocytes do not function properly. Suspect granulocyte **dysfunction** if the patient has an adequate absolute neutrophil count (ANC) but has a history of recurrent staphylococcal skin infections, lung infections, and/or lymphadenitis.

## Febrile Neutropenia

### Evaluation

The most important part of the evaluation is the physical exam with concentration on the upper airway mucosa, teeth, eyes, and rectum. Because these patients do not have an adequate number of neutrophils, they may **lack** localizing signs of inflammation. **Any** rash or skin ulceration/swelling is potentially significant. Pay special attention to the placement of all foreign bodies such as catheters and implants. A thorough physical exam must be repeated every day. If you are giving treatment to increase the ANC, you may see localizing signs of infection become apparent with time and with increase in the ANC.

Initial lab evaluations of febrile neutropenia should include:

- CBC with differential
- Basic chemistries
- Liver transaminases and bilirubin
- Blood and urine Gram stain and cultures (including bacterial and fungal and through every device) +/- other appropriate sites (e.g., sputum)
- Chest radiograph (even if no lung symptoms)

Consider these tests in the appropriate circumstances:

- Lumbar puncture if the patient is confused without identifiable cause
- Fungal markers (e.g., galactomannan antigen and beta-D-glucan for *Aspergillus*)
- Bronchoscopy or open lung biopsy for pathology, Gram stains, and bacterial/viral/fungal cultures in patients with pulmonary infiltrates
- Skin biopsies for pathology and bacterial + fungal smears and cultures

### Empiric Treatment

When a neutropenic patient presents with **fever**, you must initially cover for **gram-negative** organisms. Antibiotic regimens recommended by the Infectious Diseases Society of America (IDSA) were most recently updated in 2010 and have shifted empiric treatment of febrile neutropenia to now recommend **monotherapy** with 1 of these agents as the best choice:

- Piperacillin-tazobactam
- Carbapenem (imipenem or meropenem)
- Cefepime

Vancomycin is usually added to the above empiric regimens if any of the following are present:

- Hypotension or other evidence of severe sepsis
- Positive blood culture for gram-positive bacteria (before organism/susceptibility is discerned)
- Pneumonia documented radiographically
- Persistent fever while on empiric antibiotics
- Obvious skin infection or erythema at the site of an indwelling catheter
- History of MRSA infection or known colonization
- Severe mucositis if quinolone prophylaxis has been given **and** ceftazidime (which is not usually used now) is employed as empiric therapy

Know which gram-positive organisms are **not** covered by vancomycin:

- *Leuconostoc*
- *Lactobacillus*
- *Pediococcus*
- Vancomycin-resistant *Enterococcus* (VRE)

Worry about these organisms if the patient has persistent fever and neutropenia while on empiric vancomycin; however, the first 3 are fairly uncommon. VRE is a much greater clinical problem.

If vancomycin is included in the initial regimen, it is usually discontinued after 2 days if there is no evidence of a gram-positive infection.



## Quick Quiz

- What are some differences between Th1, Th2, and Th0 T-cell subsets?
- Name some factors that affect whether a patient with neutropenia develops an infection.
- What are your options for empiric treatment of the febrile neutropenic? When is vancomycin included?
- What gram-positive organisms are not covered by vancomycin?
- What organisms are not covered by caspofungin?
- In the empiric treatment of febrile neutropenia, when would you want to choose voriconazole or liposomal amphotericin B over caspofungin?
- What is the most common inherited immunodeficiency?
- What is unique about IgA deficiency in regard to pregnancy tests?

If the fever and neutropenia persists after 4–7 days on empiric antibiotics (including vancomycin), add:

- an echinocandin (**caspofungin** is the only one FDA-approved for this indication; fewer side effects than amphotericin B),
- liposomal amphotericin B, or
- voriconazole.

Know the organisms that are **not** covered (or probably not covered) by the echinocandins:

- *Cryptococcus*
- Resistant yeasts (*C. parapsilosis*, *C. guilliermondii*)
- *Fusarium*
- Filamentous molds (*Mucor*)
- Endemic fungi (histo, blasto, cocci)
- *Aspergillus* (For aspergillosis the situation is a little complicated; echinocandins have been used successfully, albeit mostly in salvage and combination regimens.)

Worry about these organisms if the patient has persistent fever and neutropenia while on an empiric echinocandin.

Know that fluconazole should **not** be used as an empiric antifungal because:

- clinical trials show it doesn't work, and
- it is ineffective against *Aspergillus* and some resistant yeasts (*C. glabrata*, *C. krusei*).

Regarding which specific antifungal to choose, usually it doesn't matter, **except** in the following circumstance: Definitely choose voriconazole or liposomal amphotericin B in the patient with a pulmonary presentation consistent with invasive pulmonary **aspergillosis**.

Empiric antifungal coverage will resolve the fever in about 1/2 of patients. It is problematic, however, because resolution of fever on an antifungal drug does not necessarily mean the patient has a fungal infection. Duration of treatment is often a problem. Note: Patients with acute myeloid leukemia (AML) have a markedly increased risk of developing *Aspergillus* infection.

### Prophylaxis and Adjuvant Treatment

According to the 2010 IDSA guidelines, prophylactic antibiotics (e.g., ciprofloxacin and levofloxacin) should be considered for those at high risk of infection, particularly those with expected neutropenia duration > 7 days with an ANC ≤ 100 during this time period.

In these same guidelines, colony-stimulating factors (e.g., G-CSF) are recommended in patients who are at risk (≥ 20% chance) of developing fever (e.g., expected long duration of neutropenia with low ANC). However, these agents are **not** recommended in treatment of established fever and neutropenia.

### HUMORAL DEFICIENCIES

Humoral deficiencies can be inherited (e.g., X-linked agammaglobulinemia, common variable immunodeficiency, IgA deficiency) or acquired (myeloma, ALL, CLL, HIV/AIDS, asplenia).

#### Inherited Deficiencies

The inherited disorders usually present in childhood, and these patients are typically not in the care of the general internist. Diseases are diagnosed by measuring total levels of immunoglobulins G, A, and M.

Know that **selective IgA deficiency** is the **most common** inherited immunologic defect. Most patients have **no** symptoms. Symptomatic patients present with recurrent **sinopulmonary** disease from **encapsulated** organisms, recurrent **giardiasis**, and food/respiratory allergies. These patients often form autoantibodies and may have **auto-immune** diseases such as Hashimoto's, celiac disease, pernicious anemia, systemic lupus erythematosus (SLE), and rheumatoid arthritis.

Know these 3 important facts about selective IgA deficiency:

- 1) Women can have false-positive **serum** pregnancy tests (urine pregnancy test is normal).
- 2) Blood transfusion is associated with a higher-than-normal risk of anaphylaxis and should be avoided if possible. Theoretically, the patients have anti-IgA antibodies, and transfused blood contains small amounts of IgA.
- 3) IVIG is contraindicated for the same reason as blood transfusion.

### Acquired Deficiencies

Acquired deficiencies are common clinical scenarios for the general internist. Infections arise because either effective antibodies are not produced or the B and T cells are not communicating effectively with one another. Most of these diseases are associated with **hypogammaglobulinemia** (reduction in levels of specific IgA, M, and G) but with a relative polyclonal increase in the gamma globulin fraction (i.e., patients produce an excess of fairly useless antibodies that are **not** specific for an antigen, are usually ineffective, and may cross-react with normal body components such as red cells and platelet surface receptors).

Patients with acquired **humoral** deficiencies are predisposed to infections with **encapsulated** organisms, **GNRs**, and **giardiasis**. Recurrent giardiasis (x3) should trigger a workup for this.

The spleen clears out bacteria and is the site for formation of opsonizing antibodies. Opsonizing antibodies are important in defending the host from infection with **encapsulated** organisms, especially **pneumococcus**. Splenectomy increases the risk of overwhelming **pneumococcal**, **malarial**, and **babesial** infections. The latter 2 are both intra-RBC protozoan parasites.

IgA blocks viral attachment to mucosal surfaces, and IgG blocks viral attachment to **host** cells.

### COMPLEMENT DEFICIENCY

The complement cascade and complement deficiencies are discussed in the Allergy & Immunology section, Book 4. Deficiencies result in an increased risk of infection and autoimmune disease.

Let's review a summary of the complement deficiencies and the types of infections that tend to occur in each.

#### Classical Pathway Deficiencies

C1, C2, and C4 deficiencies: recurrent sinopulmonary infections +/- otitis media with encapsulated bacteria, specifically pneumococcus, *H. influenzae*, and *Neisseria*. These deficiencies are associated with development of systemic lupus at an early age.

C3 deficiency: severe infections with pneumococcus and *H. flu* from infancy.

C5–C9 deficiencies ("terminal complement deficiency"): recurrent *Neisseria* infections (meningococcus and gonococcus). Thus, these patients often have recurrent meningo- and gonococcemia. Usually the presentation is mild or moderate—mortality from these infections in this group of patients is low.

Screen patients for classical complement deficiencies if they have had recurrent bacterial infections and a workup showing a normal CBC and immunoglobulins **or** repeat neisserial infections (or someone in their family has). The screening test of choice is the CH50,

sometimes also called "total hemolytic complement," or THC. Deficiency causes an undetectable CH50 titer. Once the CH50 is established as abnormal, measure each individual complement component to determine the specific deficiency. [Know.] C2 deficiency is the **most** common, and terminal deficiencies are **least** common, so start with measurement of C2.

### Acquired Classical Deficiencies

[Know.] Certain systemic diseases that activate complement are associated with an increased risk for infection as a result:

- Systemic lupus erythematosus
- Mixed cryoglobulinemia due to chronic hepatitis B (HBV) or hepatitis C (HCV)
- Some vasculitic diseases (polyarteritis nodosa)
- Some primary renal glomerulonephritides, even when systemic complement levels are not that low

End-stage liver disease is also associated with clinically significant hypocomplementemia because the liver cannot synthesize the proteins.

### T-CELL DEFICIENCY

T-cell-deficient patients are said to have decreased "cellular" immunity. T-cell defects occur in the following:

- HIV/AIDS
- Hodgkin lymphoma if T-cell-derived
- T-cell variant of ALL
- Prolonged corticosteroid use
- Solid organ transplantation (because of immunosuppressant Rx)

Patients with T-cell defects are more susceptible to routine **community-acquired** bacteria and viruses (pneumococcus, *Mycoplasma*, *Legionella*, *Listeria*, *Salmonella*, influenza, respiratory syncytial virus [RSV]) and **opportunistic** infection (OIs) with the following pathogens:

- Bacteria (*Nocardia*, *Rhodococcus equi*, mycobacteria)
- Viruses (especially new infections with cytomegalovirus [CMV], herpes simplex [HSV], varicella zoster [VZV])
- Fungi (*Pneumocystis*, *Cryptococcus*, *Aspergillus*)
- *Strongyloides*

Patients also frequently reactivate protozoal and viral diseases that they have previously held under immunosuppression with T cells:

- *Toxoplasma gondii*
- CMV, HBV, HCV, VZV, HSV, papillomavirus, and BK polyomavirus



## Quick Quiz

- Splenectomy predisposes a patient to worse infection from what organisms?
- Patients with which complement deficiencies are at risk for *Neisseria* infections?
- What test is used to screen for complement deficiencies?
- Review the infections associated with solid organ transplants and when each is likely to occur.

### Solid Organ Transplantation

In addition to the previous, patients who have received a solid organ transplant are also at risk for infections that come with the new tissue, as well as nosocomial infections. Additionally, as they progress in immunosuppression from their anti-rejection drugs, patients can reactivate infections that had been previously controlled by their immune system. Some of these infections are mentioned above but also include endemic fungi and mycobacteria.

As mentioned, these patients have decreased **cell-mediated immunity** due to immunosuppressive drugs. These drugs are also associated with significant toxicity if levels are not properly monitored. Certain infections tend to occur in these patients during a fairly specific period of time after the transplant.

Know the following **classic** 3 post-transplantation time periods and their associated infection risks:

- Month 1: Infections from the donor; nosocomial infection (specific to the type of surgery performed).
- Months 2–6: Immunosuppressant medication is starting to take effect, and patients are at risk for the OIs described above. CMV from donor+/recipient– solid organ transplant recipients.
- > 6 months: Community-acquired infections.

However, the use of routine prophylaxis with TMP/SMX and valganciclovir has shifted the time of onset of some OIs. For instance, CMV may not occur until > 6 months in these patients.

### HIGHLIGHTS

[Know.]

Inherited humoral deficiency of IgA:

- Sinopulmonary infections with encapsulated organisms
- Giardiasis
- Food and inhalant allergies
- False-positive **serum** pregnancy tests
- Anaphylaxis with blood transfusion and IVIG

Acquired humoral deficiencies: splenectomy, leukemias, lymphomas, myeloma, HIV/AIDS, encapsulated organisms.

Classical complement deficiencies: sinopulmonary infections with encapsulated organisms, C2 deficiency that is associated with SLE.

Terminal complement deficiencies: encapsulated organisms, meningococcemia.

T-cell defects: HIV/AIDS, post-transplant, corticosteroids, fungi, acid-fast bacteria, viruses, parasites.

## ANTIBIOTIC THERAPY

### HOW ANTIBIOTICS WORK

Most antibiotics work by affecting protein synthesis (Figure 2-1), folate metabolism, the cell wall, or the cell membrane. First, let's review protein synthesis.

#### Review: Protein Synthesis

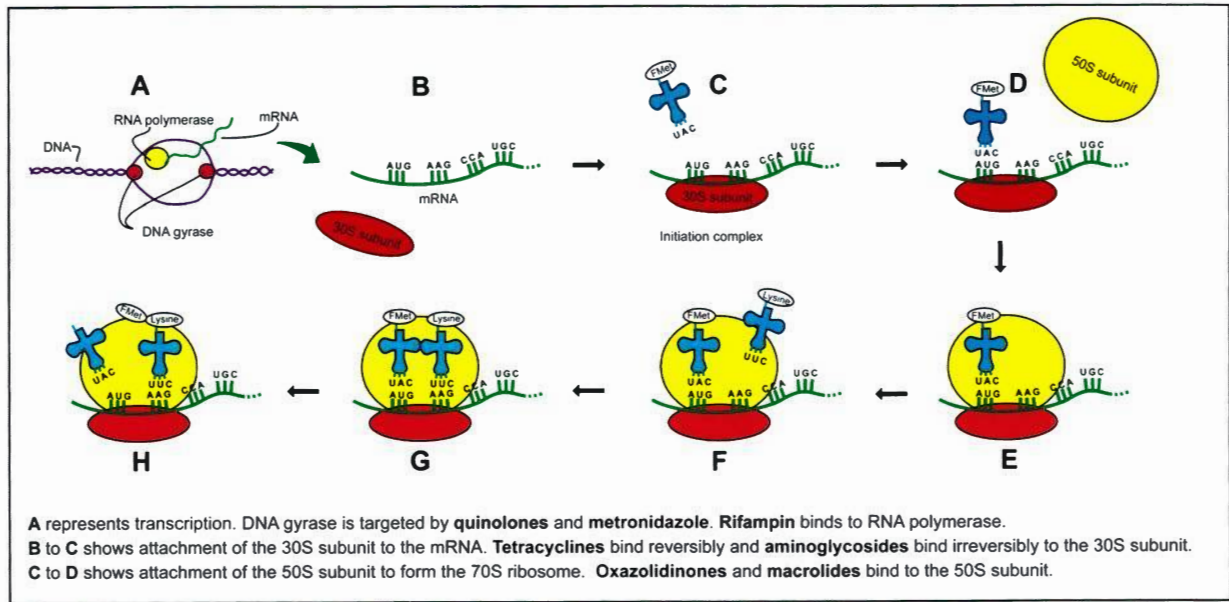
**Transcription.** The DNA particle must be unwound from its supercoiled arrangement before it can be “read” by RNA polymerase. This involves cutting the strand, holding onto the cut ends to prevent them from being damaged, allowing the double helix to uncoil and the DNA to be copied, and then precisely gluing the cut ends back together again. The key enzyme that carries out this process in bacteria is **DNA gyrase**.

RNA polymerase moves along a section of DNA (a gene), uncoiled by the DNA gyrase and, following the coded messages on the deoxyribonucleotides, forms a string of complementary-paired ribonucleotides; i.e., a piece of RNA—more specifically, pre-mRNA. With the removal of an intron, the pre-mRNA becomes mRNA (messenger RNA). This is called transcription because the DNA code is transcribed into a complementary RNA code.

**Translation.** Ribosomes are the translation units that convert the coded message in the mRNA to a specific sequence of amino acids. A 30S ribosomal subunit attaches to the mRNA at the “ribosome binding site,” then moves along the RNA until the RNA reaches the start codon (AUG). Here, a tRNA (with anticodon UAC), carrying an altered methionine (f-Met), binds with this subunit and mRNA to form the “initiation complex.” A 50S ribosomal subunit then comes along and binds to this complex to form the 70S ribosome.

Amino acid-specific transfer RNAs (tRNA) attach to the 20 amino acids used in making protein. The bottom loop of these “inverted cloverleaf-shaped” tRNAs has 3 unpaired bases called anticodons.

As the 70S ribosome moves along the mRNA, tRNAs attach one at a time, bringing these amino acids with them. These amino acids are bound together, forming a gradually lengthening protein chain.



**Figure 2-1: Antibiotic Effects on Protein Synthesis**

When the ribosome reaches the end of the coded message, translation stops. The ribosomal subunits then separate and detach from the mRNA, and the completed protein is released.

### Antibiotics that Block Protein Synthesis

**Rifampin** binds to RNA polymerase and blocks initiation of the transcription of DNA to mRNA.

**Quinolone** antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin) specifically target the DNA gyrase of bacteria. This allows the DNA gyrase to cut the double helix but then prevents the cut ends from being rejoined.

**Metronidazole**, a very important antianaerobic and antiprotozoal agent, probably has a primary mode of action similar to the quinolones, although it also affects cell membrane function.

**Aminoglycosides** (e.g., gentamicin, amikacin) bind irreversibly to the 30S subunit and prevent the 50S subunit from attaching.

**Tetracyclines** (e.g., doxycycline) bind reversibly to the 30S subunit, distorting it so that the anticodons of the tRNAs cannot align properly with the codons on the mRNA.

**Macrolides** (e.g., erythromycin, azithromycin) bind reversibly to the 50S subunit. They prevent peptide bond formation between the amino acids and, hence, keep the 70S ribosome from translocating down the mRNA.

**Clindamycin** works very similarly to macrolides.

**Oxazolidinones** (e.g., linezolid) and streptogramins bind to the 50S ribosomal subunit, thereby preventing attachment to the initiation complex.

**Trimethoprim** and the **sulfonamides** block the production of folic acid from para-aminobenzoic acid (PABA). Folic acid is required to replicate DNA.

### Review: Cell Wall Synthesis

Peptidoglycan is a component of bacterial cell walls. It is composed of alternating polysaccharides: N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). Cross-links exist between the alternating strands so that the wall is solid. NAG and NAM (and their cross-links) vary slightly between gram-positive and gram-negative organisms.

Gram-negative organisms have an **outer membrane** (OM) outside of the **cell wall**.

### Antibiotics that Affect the Cell Wall

A variety of antibiotics act at one or more stages of peptidoglycan synthesis. In order for an antibiotic to affect the cell wall of gram-negative organisms, the drug has to pass through the OM—passage is affected by drug size and charge. Thus, some gram-negative organisms have inherent resistance to certain cell wall agents that are less able to pass through the OM.

**Beta-lactams** are a class of antibiotics that interrupt formation of the bacterial **cell wall**. Because there is no analogous structure in human cells, relatively high doses can be administered. However, idiosyncratic reactions may occur with beta-lactams. Especially remember penicillin allergy, anaphylaxis, and acute interstitial nephritis.

**Vancomycin** works by inhibiting cell wall synthesis of gram-positive organisms. **Telavancin** (a synthetic derivative of vancomycin) works on inhibiting cell wall synthesis and also disrupting the cell membrane.



## Quick Quiz

- Which antibiotics target DNA gyrase to interrupt protein synthesis?
- Which antibiotics antagonize folic acid?
- How are gram-negative organisms inherently more resistant to antibiotics, compared to gram positives?
- Which group of antibiotics affects the developing bacterial cell wall?
- How does disk diffusion testing help you?
- What is the specific definition of MIC and MBC?

### Antibiotic that Affects the Cell Membrane

**Daptomycin** inserts into the cell **membrane** of gram-positive bacteria, creating a channel that allows for efflux of ions and disruption of membrane polarization.

## IMPORTANT PHARMACODYNAMICS

### Overview

What happens to those blood, urine, and goop samples in the lab?

### Important Basic Microbiology

Bacteria can be directly visualized with Gram stain and then grown in a liquid medium. Some specimens are placed directly in liquid (without a Gram stain first) if they are **not** known to be certainly infected (e.g., urine). The liquid medium is incubated for 24 hours and observed for development of turbidity, which would indicate bacterial growth.

Once bacterial growth is established, identification and sensitivity are done. **Traditionally**, the culture would then be plated on various agar plates to identify the bacteria, and disk diffusion susceptibility would be done to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the drug for those bacteria (see below).

Most hospitals currently use an **automated** system that performs identification and sensitivity simultaneously, usually by a **microtiter** method.

Disk diffusion (Kirby-Bauer) testing is now used for specific, difficult-to-treat bacteria that do not grow well in the automated media or for testing with antibiotics that are not included in the standard panels.

### MIC and MBC

[Know.] The **MIC** is the concentration of antibiotic that inhibits **visible growth** (visible turbidity) *in vitro* after 24 hours of incubation. At the 24-hour assessment, some

of the broth dilutions that have a higher concentration of drug than the MIC still have organisms growing in them—just not in sufficient numbers to cause turbidity. But, if you subculture the non-turbid cultures that contain higher concentrations of drug for another 48 hours and then reassess growth, you can determine the minimum bactericidal concentration (MBC). The **MBC** is the concentration of drug that **inhibits 99%** of the initial inoculum.

An alternative way of testing MIC is with the Epsilon meter test (Etest) strip, which uses a gradient of multiple concentrations of an antibiotic on a strip placed on the lawn of the bacteria growing on the agar.

If your patient has a critical bacterial infection, which concentration of antibiotic do you aim to deliver to the site of infection—the MIC or the MBC? Of course, you would prefer the MBC—because you want 99.9% of the infection eradicated. The problem is that the MBC is costly and time-consuming, so most microbiology labs do not routinely report the MBC; they report only the MIC. However, as a general guideline, the MBC is ~8–10x the MIC.

The usual drug dosages take the typical MICs and MBCs into account, so you generally don't need to use this information. However, in cases with **complicated** or **serious** infections, this information could be very helpful. Look at pharmacologic tables to determine the serum (or tissue) concentrations that result from specific drug doses. One place to find this information is the Pharmacologic Features section of the Sanford Guide. Next, determine if the dose you have chosen will result in a concentration that is around 8–10x the MIC (i.e., the probable MBC) at the patient's site of infection. This information helps you pick the best dose to treat the infected area. A caveat to this approach is that you almost never know the concentration of an antibiotic at the actual site of infection.

### General Rules of Antibiotic Use

Know these important points:

- Source control is generally considered key to treating serious infections. If pus can be drained, do it. Lines, catheters, and devices may need to be removed.
- Pick the drug with the proper spectrum for the bacteria and the site of infection.
- Adjust dosage for body size and renal clearance when appropriate.
- Know what to expect. If the patient doesn't respond as expected, think: Is the patient getting the drug? Is there resistance? Is there a hidden pus pocket?
- Know the difference between concentration-dependent (dose-dependent) killing and concentration-independent (time-dependent) killing (next).

### Concentration-dependent Killing

Concentration-dependent killing means that killing increases as you increase the concentration of drug above the MIC for the bugs you are treating. This is sometimes referred to as “dose-dependent” killing because killing is based on **concentration** above MIC, not on time. Aminoglycosides and quinolones are drugs that exhibit concentration-dependent killing.

Quinolones and aminoglycosides also exhibit a **post-antibiotic effect** (PAE). A PAE is persistent killing of bacteria even after the concentration of drug has fallen below the MIC at the site of infection. The dose-dependent killing and PAE allow these drugs to be dosed once daily, achieving a high peak concentration.

### Concentration-independent Killing

In concentration-independent killing, the concentration of drug above the MIC does not really matter. Instead, killing is related to how **long** the concentration of antibiotic remains greater than the organism’s MIC at the site of infection (termed “time over MIC”). This is sometimes referred to as “time-dependent” killing because killing is based on **time** (not on concentration). Beta-lactams are such drugs. Aim for serum concentrations above the MIC for > 50% of the dosing **interval**.

Because beta-lactams are time-dependent, it is not as important to aim for 8–10x the MIC with dose. Instead, patients need repeated, reliable dosing so they don’t have periods during the dosing interval when their serum levels fall below the MIC.

The clinical relevance is that, with concentration-independent killing, patients who **miss** doses have a serious risk of **treatment failure**.

## BETA-LACTAM ANTIBIOTICS

### Overview of Penicillin

The first of the beta-lactam antibiotics was penicillin (PCN). PCN antibiotics are less confusing and easier to remember if you understand that drugs were created either to increase the **spectrum** of activity or to address **developing resistance**.

The development timeline of these drugs is:

PCN → Semisynthetic PCNs → AminoPCNs → Extended-spectrum PCNs → AminoPCN/Extended-spectrum PCNs + beta-lactamase inhibitors (BLIs)

### Development of PCNs

The next topic area covers the penicillin-based antibiotics using the above development timeline, starting with PCN.

#### Penicillin

The drug was first mass produced and used effectively during World War II to treat war wounds. Today, **PCN**

is appropriate mainly for streptococci, sensitive enterococci, and syphilis. It has decent activity against gram-positive skin flora and some mouth anaerobes, but poor activity against gram negatives and gut anaerobes.

Staphylococci rapidly developed resistance by producing penicillinase, a beta-lactamase enzyme that destroys the drug. These resistant staph are referred to as “methicillin-sensitive” because they were sensitive to the next major drug class to come along ...

### Semisynthetic Penicillins

**Methicillin** (and later, **oxacillin**; today we also have **nafcillin** and **dicloxacillin**): These drugs are called “semisynthetic penicillins” and are more stable against penicillinase. They are drugs of choice for methicillin-sensitive staphylococci (*S. aureus* [MSSA] and *S. epidermidis* [MSSE]).

Today you only **rarely** encounter a penicillin-sensitive *Staphylococcus*, but if you do, penicillin is the drug of choice.

The semisynthetic penicillins are good for skin flora but still lack activity against gram negatives. So, the next major drug class to be developed was the ...

### Aminopenicillins

**Ampicillin** (and its oral formulation, amoxicillin): These drugs are called “aminopenicillins.” They retain the efficacy of PCN against skin flora and mouth anaerobes but also kill the “weaker” or more susceptible gram-negative organisms, such as many *E. coli*. Therefore, this new class added activity against **urogenital** and **colon** bacteria.

Unfortunately, resistance developed **quickly**; bacteria started producing other beta-lactamases. Another standing issue was that the aminopenicillins did **not** kill the more resistant gram-negative rods (GNRs) such as *Pseudomonas*. So, the next major drug class to be developed was the ...

### Extended-spectrum Penicillins

**Piperacillin** and **ticarcillin**: These drugs are called “extended-spectrum PCNs” (**ES-PCNs**) because they take the spectrum of ampicillin and extend it to cover the “mighty” GNRs, including *Pseudomonas*. The only problem with these PCNs was the rapid development of resistance via a beta-lactamase. So, the next addition to come along was the ...

### Addition of Beta-lactamase Inhibitors

Addition of a beta-lactamase inhibitor (BLI): **Sulbactam**, **tazobactam**, or **clavulanic acid**—in combination with an aminoPCN or an ES-PCN—protects the PCN from beta-lactamase hydrolysis.



## Quick Quiz

- What is the difference between concentration-dependent and time-dependent killing?
- What is a post-antibiotic effect?
- In time-dependent killing, how long should a patient's serum concentration of a drug be higher than the infecting organism's MIC?
- What is the spectrum of activity of penicillin?
- Nafcillin is the drug of choice for what infection?
- What coverage does ampicillin add over penicillin? Which important organisms does ampicillin not cover?
- Which organisms do extended-spectrum penicillins cover?
- BLIs are combined with which drugs?
- Which penicillins are the broadest in spectrum? What do they cover?
- What is a potential complication of nafcillin?

PCN + BLI combinations:

- IV ampicillin + sulbactam = Unasyn<sup>®</sup>
- Oral amoxicillin + clavulanic acid = Augmentin<sup>®</sup>
- IV ticarcillin + clavulanic acid = Timentin<sup>®</sup>
- IV piperacillin + tazobactam = Zosyn<sup>®</sup>

The drugs retain the activity of the parent PCN, but they are also effective against organisms that became resistant via a beta-lactamase. For example, Augmentin still does not cover *Pseudomonas* (because the parent aminoPCN did not cover it), but it is an effective drug against MSSA.

### Extended-spectrum PCNs + BLIs

The ES-PCNs with BLIs (Timentin<sup>®</sup> and Zosyn<sup>®</sup>) are the broadest in spectrum of all the PCNs, covering resistant GNRs, *Pseudomonas*, methicillin-sensitive staphylococci, and both mouth and gut anaerobes. Organisms that are resistant to these drugs can be very difficult to treat.

### Evolution of MRSA

Staphylococci eventually acquired the *mecA* gene, which encodes a **change** in the penicillin-binding proteins that the beta-lactams use to bind the bacteria. *MecA* transcription results in **reduced** affinity of all beta-lactams for the organisms' cell walls. The staph that express this gene are called **methicillin-resistant** staphylococci (methicillin-resistant *S. aureus* [MRSA] and methicillin-resistant *S. epidermidis* [MRSE]).

Only **vancomycin**, **daptomycin**, and **linezolid** effectively treat **serious** infections with **MRSA/MRSE**. Newer drugs with anti-MRSA activity include ceftaroline, telavancin, and tigecycline. Their exact clinical roles remain to be determined. Mild skin and soft tissue MRSA infections often retain susceptibility to clindamycin, trimethoprim/sulfamethoxazole, or doxycycline.

Next, we will discuss each type of PCN again, but in slightly more detail.

### Penicillin Again

Penicillin, as noted above, has the beta-lactam ring. It is very active against most streptococci (groups A and B, viridans group, and *S. pneumoniae*), *Pasteurella* (animal bites), *Listeria*, and many *Neisseria* species. It is also active against many anaerobes usually found **above** the diaphragm (e.g., in the mouth; *Clostridium*) but **not** those found below (e.g., *B. fragilis*). [Know:] Even though PCN is indicated for meningococcal infections, **rifampin or quinolones** are better for eradication of the **carrier state**. Rifampin concentrates in the upper respiratory mucosa.

PCN is still the drug of choice for many infections, including:

- Erysipelas due to *Streptococcus pyogenes* (group A)
- *Streptococcus agalactiae* (group B)
- Viridans streptococci (some are now resistant to PCN and ampicillin)
- PCN-sensitive *S. pneumoniae*
- *Treponema pallidum* (syphilis)
- Leptospirosis
- Actinomycosis
- *Neisseria meningitidis* (bacteremia and meningitis)

### Nafcillin and Dicloxacillin Again

Penicillinase-resistant, semisynthetic penicillins (nafcillin, oxacillin, and dicloxacillin) are used to treat methicillin-sensitive *S. aureus* because 85% of the *S. aureus* have this penicillinase. Clinically, nafcillin and oral dicloxacillin are used only to treat MSSA and MSSE.

An important potential complication of these drugs is **acute interstitial nephritis**. Remember that manifestations of interstitial nephritis are fever, eosinophilia, and rash. Eosinophils can also be found in the urine (especially on Board exams).

### Ampicillin Again

Ampicillin has a spectrum similar to PCN, but its spectrum extends to include certain gram-negative rods—especially some *E. coli*, *H. influenzae*, *Salmonella*, *Shigella*, and *Proteus mirabilis*. **However**, it does **not** cover *Klebsiella*, and many isolates of *H. influenzae*, *E. coli*, and *P. mirabilis* are resistant.

Know that ampicillin is the drug of choice for:

- *Listeria monocytogenes* meningitis
- Salmonellosis—if sensitive
- UTIs due to susceptible organisms
- Susceptible enterococcal infections

### Ticarcillin and Piperacillin Again

Piperacillin (the most commonly used extended-spectrum PCN) is more effective against the **gram-negative** organisms (including *Pseudomonas*) and **anaerobes** (including *B. fragilis*). Similar to ampicillin—only more “extended.” Remember: A beta-lactamase inhibitor can be added to ticarcillin (Timentin) and piperacillin (Zosyn) to protect the beta-lactam from beta-lactamase hydrolysis. They are the **only** PCN drugs effective against *P. aeruginosa* and *Acinetobacter*.

### Penicillin Allergy

Penicillin allergy is very commonly reported by patients. Know that you can test for this by performing skin testing; a negative skin test makes a future anaphylactic reaction to penicillin very unlikely. As an alternative, patients can also be desensitized (next).

### Desensitization

Desensitization is a simple procedure that can be done for any patient with an IgE-mediated immediate hypersensitivity reaction to a medication. Common antibiotics that can cause this reaction are the beta-lactams, quinolones, clindamycin, and aminoglycosides.

Vancomycin can also cause an IgE-mediated immediate hypersensitivity reaction. However, the “**red man syndrome**,” which occurs more commonly with vancomycin, is a **distinctly separate** reaction that is treated differently (page 2-12).

A typical desensitization procedure starts with very tiny oral or IV doses (1/1,000 to 1/10,000 x normal) and increased dosage every 15 minutes. After 4–8 hours, a full dose is reached, and a temporary tolerance to the drug is achieved. The patient can then be given the full course of the antibiotic. This tolerance is lost rapidly once the drug is stopped, so the procedure will have to be repeated if the drug is ever given again.

Note: Generally, oral doses are the preferred method, but even with oral doses, the patient must be in a monitored setting where treatment for anaphylaxis is available.

### Overview of Cephalosporins

Cephalosporins also contain the beta-lactam ring but are inherently penicillinase-resistant because of their structure. They are slightly more difficult to remember than the PCNs—probably the easiest way is to consider them based on their generation category. Then you will need to remember some special caveats about specific drugs.

Although a generalization, it is useful to remember that the spectrum of these drugs tends to widen and include more GNRs and anaerobes as the generations increase in number. Also know that, in general, cephalosporins have **no activity** against enterococci, *Listeria*, and methicillin-resistant staphylococci.

### 1<sup>st</sup> Generation Cephalosporins

1<sup>st</sup> generation cephalosporins (**cefazolin** and oral **cephalexin**) are active against most staph (including the penicillinase-producing strains) and most strep.

Cefazolin and cephalexin are unlike PCN in that they have:

- No anaerobic activity
- Some coverage against community-acquired GNRs such as *E. coli*, *Klebsiella*, and *Proteus*. (In fact, the GNR coverage is superior to ampicillin.)

1<sup>st</sup> generation cephalosporins are commonly given for:

- Skin and soft tissue infections
- Some surgical prophylaxis
- Oral treatment of mild urinary tract infections

### 2<sup>nd</sup> Generation Cephalosporins

Gram-negative coverage increases for most of these drugs, and some pneumococcal coverage is retained (**cefuroxime**). Two drugs in this group, **cefotixin** and **cefotetan**, are noteworthy for their **anaerobic** coverage. These drugs are used to treat:

- PID
- Postoperative abdominal infections

The 3<sup>rd</sup> generation cephalosporins have largely replaced the 2<sup>nd</sup> generation **except** for anaerobic infections (usually due to gut flora).

### 3<sup>rd</sup> Generation Cephalosporins

3<sup>rd</sup> generation cephalosporins are generally stable against most beta-lactamases and have enhanced activity against pneumococci, *H. influenzae*, and *N. gonorrhoeae*. The GNR coverage is also somewhat enhanced over previous generations, so these drugs are better for the *Enterobacteriaceae* (*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, and *Serratia*).

Especially remember the following facts about 3<sup>rd</sup> generation cephalosporins:

- They are great pneumococcus drugs, so they are recommended as 1<sup>st</sup> line agents for **community-acquired** pneumonia and PCN-resistant pneumococcal meningitis in combination with vancomycin for empiric treatment.
- **None** of the drugs are 1<sup>st</sup> line agents for MSSA; some, like ceftazidime, do **not** cover MSSA at all. Do **not** ever use ceftriaxone for empiric coverage of an infection that may be due to staphylococci. 1<sup>st</sup> generations or oxacillin is preferred for MSSA.



## Quick Quiz

- Which cephalosporins have anaerobic activity?
- 3<sup>rd</sup> generation cephalosporins are known for their activity against which organisms?
- Under what circumstances would it be appropriate to treat MSSA with ceftriaxone?
- What are ESBLs, and preserved susceptibility to what antibiotic is a sign of the presence of an ESBL-producing organism?
- Which beta-lactam drug can be given to patients with a penicillin allergy?
- None of the drugs cover anaerobes. 2<sup>nd</sup> generations or PCNs are better.
- Cefazidime is the only 3<sup>rd</sup> generation drug that has antipseudomonal activity.
- Three of the 3<sup>rd</sup> generation cephalosporins can cross an inflamed blood-brain barrier; therefore, they are indicated as the primary therapy for meningitis caused by *Enterobacteriaceae*. These are ceftriaxone (Rocephin®), cefotaxime (Claforan®), and ceftazidime.

### 4<sup>th</sup> Generation Cephalosporins

The 4<sup>th</sup> generation drugs could be considered the broadest in spectrum and the most stable against resistance. Cefepime has the gram-negative activity of 3<sup>rd</sup> generations and gram-positive activity of 1<sup>st</sup> generations, with enhanced stability against cephalosporinases. It has limited anaerobic coverage.

Be aware of the highly resistant organisms that produce extended-spectrum beta-lactamases (ESBLs) and cause significant infections in hospitalized patients and patients who have been repeatedly exposed to beta-lactams. ESBL production is not always present when a patient first gets the infection. It is often induced by empiric antibiotic treatment with a beta-lactam. These patients may get better initially and then get worse again as their isolate begins to turn on the resistance genes and make ESBLs. However, a clue to the presence of an ESBL isolate is the selective *in vitro* susceptibility to cefepime, when the isolate is resistant to all other beta-lactams. Currently, a carbapenem (imipenem or meropenem) is the drug of choice for empiric ESBL therapy.

### 5<sup>th</sup> Generation Cephalosporins

The only 5<sup>th</sup> generation cephalosporin currently FDA-approved is ceftaroline (Teflaro®). Its main advantage is that it is the only cephalosporin that covers MRSA. Importantly, it cannot be used to treat *Pseudomonas* infections.

## Monobactams

Aztreonam is a monobactam beta-lactam that covers only gram-negative bacteria, including *Pseudomonas*. Its spectrum is similar to aminoglycosides and 3<sup>rd</sup> generation cephalosporins. It is not active against gram-positive cocci or anaerobes. This drug can be used in patients with beta-lactam allergy, which is its niche.

## Carbapenems

### Overview

Imipenem, meropenem, and doripenem are broad-spectrum beta-lactams recommended only for use in complicated infections involving multiple organisms (such as in the abdomen or the diabetic extremity with possible bacteremia) and for empiric treatment of the very sick.

### Carbapenemases

Carbapenemases are carbapenem-hydrolyzing beta-lactamases that confer carbapenem resistance. Various forms of these have been identified over the last several years.

Be aware that very resistant GNR isolates with carbapenemases are emerging from India and Pakistan—with resistance to all beta-lactams, including the carbapenems. These very resistant organisms sometimes colonize the GI tracts of individuals who live in these countries. Generally, we rely on the carbapenems to provide coverage for the most resistant organisms, so this discovery is very discouraging.

The most critical characteristic of these very resistant organisms is their predilection for spreading—causing community-acquired infections (especially *E. coli*) and nosocomial infections (especially *K. pneumoniae*). It is postulated (and feared) that a 2-pronged worldwide epidemic might develop if these 2 organisms start spreading via these routes. Since fall of 2010, the CDC has been chronicling isolates found in the U.S.

### Imipenem

Imipenem covers most organisms: gram-positive cocci (GPC); GNRs, including *Pseudomonas* and other resistant GNRs; mouth and gut anaerobes (*B. fragilis*). It also is effective against ESBL-producing organisms.

The few organisms resistant to it include:

- *Enterococcus faecium*,
- *Burkholderia cepacia*,
- *Corynebacterium jeikeium* (JK),
- *Stenotrophomonas maltophilia*,
- *Acinetobacter* species, and
- MRSA.

Also, remember that although *E. coli* and *K. pneumoniae* are typically sensitive to imipenem,

the carbapenemase-producing variety can spread easily and cause major problems.

Resistance is developing in *Pseudomonas* isolates.

[Know:] Imipenem can lower the seizure threshold, so use it **only** as a last resort in patients with seizures and advanced-stage chronic kidney disease.

Imipenem is always formulated with equal amounts of cilastatin (combo = Primaxin<sup>®</sup>). Cilastatin is an enzyme inhibitor that impairs the metabolism of imipenem in the **renal tubule**, thereby increasing its half-life to 1 hour. Cilastatin is **not** a beta-lactamase inhibitor.

### Meropenem

Meropenem is a similar carbapenem with a longer half-life, so there is no need for an enzyme inhibitor. It is also less likely to cause seizures.

### Doripenem

Doripenem is the newest carbapenem and has similar activity and pharmacokinetics to meropenem.

### Ertapenem

**Ertapenem** is a carbapenem with once-daily dosing but **no** activity against *Pseudomonas*. It is one of the few beta-lactams with good coverage of staphylococci and extended-spectrum gram-negative rods.

Because it is available as once-daily dosing, it is used for outpatient **parenteral** treatment, especially of diabetic feet, and for abdominal, pelvic, and skin and soft tissue infections.

Understand that once-daily dosing is a big deal for a beta-lactam because these drugs usually exhibit time-dependent killing; hence, most have frequent-dosing schedules.

## OTHER ANTIBIOTICS

### Vancomycin

**Vancomycin** is effective against most gram-positive organisms, including MRSA, *Clostridium*, and *Corynebacterium*. Pharmacodynamics is complicated. **Trough levels** are used for monitoring effective dosing—to guide efficacy as well as toxicity. For most infections, pre-dose levels between 15 and 20 mg/L are recommended.

Clearance of vancomycin in patients undergoing hemodialysis may vary widely depending on the machine and the membranes used, so levels are often needed to guide dosing.

Some strains of enterococci are vancomycin-resistant, and resistance is increasing in staphylococci. Know that when a staph isolate's MIC is  $> 1$  mcg/mL, experts suggest using an alternative drug to treat the infection; e.g., linezolid or daptomycin. (**Dapto** is ineffective in the

lung, however). Staphylococci with an MIC  $> 2$  mcg/mL for vancomycin are considered resistant.

Vancomycin sometimes causes the “red man syndrome,” which consists of tachycardia, flushing, occasional angioedema, and generalized pruritus. You can prevent this reaction by either slowing the infusion time or pretreating with antihistamines (but not H<sub>2</sub> blockers). Previous formulations of vancomycin had significant renal and ototoxicity; current formulations rarely cause toxicity in normal doses.

The sole indication for **oral** vancomycin is *C. difficile* (pseudomembranous) colitis. **IV** vancomycin is **not** effective in this situation.

### Oxazolidinones

**Linezolid** is the only oxazolidinone on the U.S. market.

Linezolid is a bacteriostatic agent active against **gram-positive** organisms, including MRSA and VRE (vancomycin-resistant enterococci). It has not been studied prospectively in *S. aureus* bacteremia. Linezolid is available in oral (with 100% bioavailability) and IV preparations.

The oral form of linezolid makes it a desirable alternative to vancomycin for MRSA; **however**, due to concerns about cost and developing resistance, as well as an unfavorable side-effect profile (below), this drug is a 2<sup>nd</sup> line agent for MRSA. **Vancomycin** remains the current drug of choice for **MRSA** treatment when the MIC is  $< 1$  mcg/mL. For staphylococcal isolates with MIC  $> 1$  mcg/mL, linezolid or daptomycin is recommended.

Linezolid can cause reversible **thrombocytopenia**, **anemia**, and **leukopenia**, especially if the patient has been taking it  $> 2$  weeks. It is also associated with development of a **sensory neuropathy**.

Know that linezolid can cause very serious CNS effects (**serotonin syndrome**) when used **concurrently** with selective serotonin reuptake inhibitors (**SSRIs**) and serotonin-norepinephrine reuptake inhibitors (**SNRIs**).

### Daptomycin

**Daptomycin** is a cyclic lipopeptide active against **gram-positive** organisms. It is indicated for treatment of skin and soft tissue infections, bacteremia, and right-sided endocarditis caused by MSSA or MRSA.

It is a parenteral drug with a long half-life that requires only once-daily dosing. Generally, it is reserved for resistant organisms such as MRSA and resistant *Enterococcus*. Know that daptomycin is ineffective for staph pneumonia. A potential complication of use is myopathy, so be careful with patients who are also taking a statin drug. Monitor CK levels at least weekly during use.



## Quick Quiz

- How does imipenem alter the seizure threshold?
- Ertapenem is useful for treating diabetic infections in what type of setting?
- What are potential complications of linezolid use?
- What is the drug of choice for staph pneumonia with an MIC > 1 mcg/mL?
- Aminoglycosides exhibit what type of killing?
- What can happen to a ciprofloxacin if it is dosed with a multivitamin?
- What happens to the concentration of theophylline if a patient is also prescribed erythromycin?

### Tigecycline

**Tigecycline** (Tygacil®) is the first of the new class of antibiotics called **glycylcyclines**, which are derivatives of tetracycline. It is **broad-spectrum** with activity against gram-positive organisms (including VRE, MRSA), anaerobes, and gram-negative rods. It has some coverage against ESBL-producing GNRs; however, it is **not** active against *Pseudomonas* and has reduced activity against *Proteus* and *Providencia*.

Tigecycline is indicated for complicated skin and soft tissue infections and intraabdominal infections. Give IV. Nausea and vomiting are its main side effects.

### Aminoglycosides

Aminoglycosides (AGs; **gentamicin** is classic example) are effective against:

- aerobic GNRs (but **not** anaerobic GNRs such as *B. fragilis*),
- *Yersinia pestis* plague (streptomycin),
- *Francisella tularensis* (streptomycin or gentamicin),
- *M. tuberculosis* (streptomycin), and
- *M. avium-intracellulare* (amikacin).

AGs are also used to treat patients with febrile neutropenia, in combination with a 3<sup>rd</sup> generation cephalosporin or an ES-PCN + BLI.

These drugs exhibit concentration-dependent killing and a post-antibiotic effect. Hence, they are best dosed once daily after a loading dose.

Potential complications of use include **oto- and nephro-toxicity**—more likely if amphotericin B is also used.

### Fluoroquinolones

**Ciprofloxacin**, **levofloxacin**, and **moxifloxacin** are the most commonly used quinolones.

Think of ciprofloxacin as a **gram-negative only** agent, with excellent *Pseudomonas* activity. It is the only oral quinolone. Ciprofloxacin should **not** be used for empiric *S. pneumoniae* coverage. On the other hand, levofloxacin and moxifloxacin **are** approved for *S. pneumoniae*.

Moxifloxacin is less active than the others against GNRs, but it is the most active quinolone for *M. tuberculosis*.

The oral bioavailability of these agents is comparable to the IV formulations.

Know the following side effects, complications, and contraindications of quinolones:

- They are chelated by cations ( $Mg^{+2}$ ,  $Ca^{+2}$ ), so certain vitamins and laxatives may **reduce** their absorption.
- They can increase theophylline levels.
- Do not give to pregnant/lactating patients or children. (FDA says no one < 18 years of age; except ciprofloxacin is now approved for 2<sup>nd</sup> line therapy in children with UTIs.)
- Do **not** use them to treat **MRSA**, even if susceptibility testing shows that the isolate is sensitive—because of the widespread, rapid development of resistance.
- Quinolones predispose for **tendonitis** and **tendon rupture** (especially the Achilles tendon in older adults).

### Macrolides

**Erythromycin** is effective against:

- *Mycoplasma pneumoniae*,
- *Chlamydophila pneumoniae*,
- *Campylobacter* (diarrhea),
- diphtheria, and
- pertussis.

It is less effective against *H. influenzae* and is **not** effective against Q fever (*Coxiella burnetii*), which you would treat with tetracycline.

Erythromycin increases the concentrations of theophylline, cyclosporine, and warfarin.

**Azithromycin** has better *S. pneumoniae* and *H. influenzae* coverage than erythromycin. It comes in both IV and oral formulations and has a very long half-life that allows for once-daily dosing.

### ANTIVIRAL AGENTS

**Acyclovir** is a nucleoside analog used for the treatment of herpes simplex and varicella-zoster viruses. Treatment of zoster infections requires higher doses.

**Valacyclovir** and **famciclovir** are oral formulations that treat herpes simplex and varicella-zoster infections. Only acyclovir is intravenous and is used to treat severe

infections. Valacyclovir and famciclovir drugs are used primarily for less-frequent dosing of outpatients.

**Ganciclovir** is used to treat **CMV** infections in post-transplant patients and those with HIV/AIDS. Typical infections are retinitis, encephalitis, pneumonitis, and colitis. This drug is preferred over foscarnet and cidofovir. Leukopenia is a side effect. Know that acyclovir resistance predicts resistance to ganciclovir as well.

**Valganciclovir** is an oral preparation similar to ganciclovir but with better absorption, leading to blood levels comparable to IV ganciclovir.

**Foscarnet** is used in patients with ganciclovir-resistant herpes infection, or as an alternative to ganciclovir for CMV. Foscarnet toxicity includes significant electrolyte and calcium derangements and renal failure.

**Ribavirin** is used as part of combination therapy for hepatitis C.

**Amantadine** and **rimantadine** treated influenza A in the past but are no longer recommended because of resistance (unless you are certain your strain is susceptible). They are ineffective against influenza B. Occasionally, these drugs are useful against oseltamivir-resistant flu A. Side effect is CNS toxicity, especially with amantadine.

**Oseltamivir** and **zanamivir** are neuraminidase inhibitors that are effective against influenza A and B. They are the drugs of choice for empiric treatment of influenza and for amantadine-resistant flu A. Some strains of influenza A have developed resistance to oseltamivir, but it is still considered the recommended drug for empiric treatment (+/- amantadine, depending on local resistance patterns).

See page 2-44 for the antiretroviral medications.

## ANTIFUNGAL AGENTS

There are 4 major classes of antifungal medicines: **polyenes**, **imidazoles**, **triazoles**, and **echinocandins**.

### Polyenes (Amphotericin Preparations)

**Amphotericin B** deoxycholate **used to be** the standard treatment for most systemic mycoses. Currently, it has been mostly replaced by lipid polyene formulations, echinocandins, and azoles. It is given IV only and has many side effects: fever, renal failure, phlebitis, acidosis, and low  $K^+$  and  $Mg^{2+}$ . Infusion-related chills and fevers ("shake and bake") may be severe. Some recommend giving a test dose first. Hypotension with the 1<sup>st</sup> dose may occur (decrease in peripheral vascular tone). Electrolyte abnormalities include hypokalemia and hypomagnesemia due to development of renal tubular acidosis.

**Lipid-associated** amphotericin B preparations are **less nephrotoxic and have less infusion-related side effects**, but are much more expensive. They are used primarily when toxicity has become a problem with amphotericin

deoxycholate preparation. However, lipid preparations may be better for some fungal infections, especially those that enter the reticuloendothelial system, such as cryptococcal meningitis and disseminated histoplasmosis. Lipid amphotericin B is also used to treat zygomycosis (*Mucor* and *Rhizopus*) because you can give higher doses of the preparation without getting the nephrotoxicity.

**Topical** polyene macrolides are **nystatin** and **amphotericin B**. These are effective **only** against mucocutaneous candidiasis (not ringworm). Both are also available in liquid form for oral and esophageal candidiasis.

### Imidazoles

**Ketoconazole** is an oral and topical preparation that is **rarely** used because there are better drugs now. Increased gastric pH (low acid) decreases oral absorption, so do **not** prescribe to patients taking  $H_2$  blockers or proton pump inhibitors (PPIs). Ketoconazole does **not** penetrate CSF well and increases levels of indinavir and digoxin, with potentiation of benzodiazepines. Side effects of oral medication include nausea and **hepatitis**. It also causes a decrease in androgen production; hence, patients may have decreased libido, and males may get gynecomastia.

Ketoconazole has many—sometimes dangerous—interactions with common drugs. For serious fungal infections, it has largely been **replaced** by **fluconazole** or **itraconazole**. It is used rarely to treat refractory tinea infections.

**Clotrimazole** and **miconazole** are available in both cutaneous and vaginal preparations. Many other preparations are also available. All are effective in the treatment of cutaneous candidiasis, tinea versicolor, and ringworm.

### Triazoles

**Itraconazole** is a triazole analog of ketoconazole and is generally more effective and safer. Capsules should be taken with food; a cola drink (acidity) will help with absorption. Levels should always be checked when using itraconazole. The liquid formulation has much better bioavailability, but food decreases absorption, so take liquid on an empty stomach. Indications include endemic fungi (histoplasmosis [including chronic suppressive therapy for disseminated disease], blastomycosis, coccidioidomycosis, and cryptococcosis), oral and esophageal candidiasis (especially if fluconazole-resistant), and sporotrichosis.

**Fluconazole** is indicated for oral and esophageal candidiasis, candidemia (for susceptible isolates), disseminated candidiasis, cryptococcosis (including suppression of meningitis), and vulvovaginal candidiasis. It has excellent penetration into the CSF. It should **never** be used as empiric antifungal treatment in febrile neutropenic patients. Know the candidal species that are either entirely resistant (*C. krusei*) or have some degree of resistance (*C. glabrata*). Be aware that the drug has many interactions. Check before prescribing.



## Quick Quiz

- What is the drug of choice for empiric treatment of influenza A?
- Liposomal amphotericin B preparations are used in what circumstances? Against which fungi?
- Which candidal species are resistant to fluconazole?
- What are the indications for voriconazole?
- What are the indications for caspofungin?

**Voriconazole** is a triazole with an extended antifungal spectrum, including *C. glabrata* and *C. krusei*, *Aspergillus*, *Fusarium*, and *Scedosporium* (*Pseudallescheria*). The drug can be given orally or IV. Voriconazole is 1<sup>st</sup> line therapy for invasive aspergillosis. Major toxicity is transient, reversible **visual** distortion and disturbance. Check voriconazole serum levels whenever you are treating a serious infection because significant variations in levels occur from person to person.

**Posaconazole** is the newest triazole with the extended antifungal spectrum of voriconazole, but spectrum includes activity against the **zygomycetes** (e.g., *Rhizopus*, *Mucor*). It is FDA-approved for prophylaxis of *Aspergillus* and *Candida* infections in those with severe immunocompromised states, including prolonged neutropenia or stem cell transplant recipients with graft-versus-host disease. It may be used for treatment of oropharyngeal candidiasis, particularly organisms refractory to itraconazole or fluconazole; invasive *Aspergillus*; and zygomycetes. It is an oral agent that requires tid or qid dosing. Check posaconazole levels, and make sure that patients take it consistently with a high-fat meal.

**Terconazole** is the only **vaginal** triazole formulation for vulvovaginal candidiasis. **Oral fluconazole** is very effective as a single dose and is usually used instead of topical agents.

### Echinocandins

Echinocandins inhibit beta-1,3-glucan, an essential component of the cell walls of several fungi, including *Aspergillus*.

**Caspofungin** acetate is approved for candidemia and candidal infections of the abdomen, peritoneum, pleural space, and fluconazole-resistant esophagitis; and for invasive aspergillosis in severely immunocompromised patients who are intolerant of lipid amphotericin B or voriconazole.

**Micafungin** (Mycamine®) is similar to caspofungin but does not require a loading dose and seems to have fewer drug interactions.

**Anidulafungin** (Eraxis™), the newest echinocandin, has similar activity to the other agents.

Most experts use an echinocandin as their **drug of choice** for empiric antifungal therapy in **febrile neutropenic** patients.

### Other Antifungals

**Flucytosine** (5-fluorocytosine; 5-FC) is highly soluble and penetrates well into the CSF. Upon entering a fungal cell, it is metabolized to the antimetabolite 5-fluorouracil. If used alone, drug resistance develops quickly.

**Amphotericin B**, used in combination with **5-FC**, both decreases drug resistance development and has a synergistic antifungal effect. This combination is used to treat cryptococcosis and **serious** forms of candidiasis.

Note that 5-FC can cause serious GI, hepatic, renal, and **bone marrow** toxicities—the latter usually presents as neutropenia and thrombocytopenia. Slight decreases in **renal function** can increase 5-FC to **toxic** levels.

## ANTIPARASITIC DRUGS

**Praziquantel** (Biltricide®) is the **only** drug effective against **all** species of *Schistosoma*. It is effective against flukes and tapeworms. It is used to treat neurocysticercosis caused by the pork tapeworm *T. solium*.

**Albendazole** is now used for cysticercosis and schistosomiasis.

**Niclosamide** is also used for the treatment of tapeworm, but it affects only those in the intestine.

**Pentamidine** is effective against *Pneumocystis jiroveci*. It is given IV for treatment or via inhalation for prophylaxis. It is not recommended as a 1<sup>st</sup> line drug because of the many side effects, including azotemia (1/4), leukopenia, pancreatitis, and hypo- or hyperglycemia.

**Nitazoxanide** is approved for treatment of *Giardia lamblia* and *Cryptosporidium parvum*.

**Antimalaria** drugs: See Malaria, [page 2-31](#).

## BACTERIA

### GRAM-POSITIVE ORGANISMS

#### Staphylococci

##### Overview

*S. aureus* causes bacteremia, especially among IV drug abusers and **dialysis** patients. In addition, it is a leading cause of hospital-acquired (**line-related**) bacteremia, and community-acquired bacteremias are also seen even in the absence of classic comorbidities. It is also a cause of toxic shock syndrome (**TSS**) and scalded skin syndrome (**SSS**; [Image 2-1](#)). *Staphylococcus* is the usual cause of **furuncles** and **carbuncles** ([Image 2-2](#)).

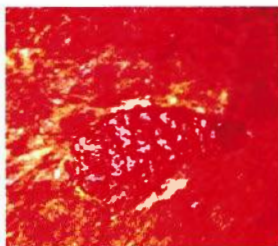


Image 2-1: Staphylococcal scalded skin synd.

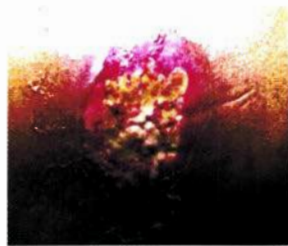


Image 2-2: Carbuncle on buttock

Pathogenicity is associated with production of entero- and exotoxins, coagulase, and leukocidin. In chronic carriers, *S. aureus* resides on the nasal mucosa.

The percentage of MRSA infections has grown substantially due to indiscriminate beta-lactam use. In most hospitals, the majority of *S. aureus* isolates are MRSA. Unfortunately, MRSA is now frequently seen in community-acquired infections as well, presenting primarily as skin and soft tissue infections, but occasionally pneumonia.

Nasal mucosal colonization is **difficult** to eradicate. The typical regimen is intranasal and under-the-nails topical mupirocin and washing with chlorhexidine (Hibiclens®) scrub.

### Toxic Shock

Toxic shock syndrome (TSS) often presents with **red skin, hypotension, fever, diarrhea, and hypocalcemia**. In young women, TSS was associated with **menstruation and tampon** use. A young woman with a uterine focus of infection at presentation may have a bloody discharge or be menstruating. Do not treat the hypocalcemia unless either symptoms or ECG signs develop. Anytime there is a post-surgical toxic shock, any device implanted during the surgery must be immediately removed (e.g., prosthetic device, implant).

Another cause of TSS is *Streptococcus pyogenes*. This usually results from a progressive skin infection—especially post-op and with chicken pox!

Note: In **staph** TSS, blood cultures are usually **negative**, whereas in **strep** TSS, blood cultures are usually **positive**!

### MRSA Treatment

MRSA bacteremia and other serious MRSA infections are initially treated with **vancomycin**. Vancomycin is typically the **drug of choice** for **skin** and soft tissue infections and invasive **MRSA**. Know that treatment failure is increasing in patients with invasive staph when the vancomycin MIC is  $> 0.5$  mcg/mL. Organisms with an MIC  $\leq 2$  mcg/mL are considered “susceptible,” but treatment failures are more common as the MIC climbs over 0.5 mcg/mL. Because of this, many ID experts are now recommending alternative drugs (linezolid or daptomycin) to treat isolates with MIC  $> 1$  mcg/mL in invasive disease. In highly resistant staph isolates (e.g., MIC  $> 2$  mcg/mL), resistance to vancomycin is often associated with daptomycin resistance as well.

Know that there are limited data for tigecycline and linezolid in MRSA **bacteremia**; so, for now, do **not** use them to treat endocarditis/bacteremia.

Linezolid is very expensive, and in general, it is not considered **except** in cases of vancomycin resistance.

### Treatment for Other *Staphylococcus aureus* Infections

In nonbacteremic, mild-to-moderate MRSA skin and soft tissue infections, other antibiotics may be effective, including TMP/SMX, clindamycin, or doxycycline. There is **rapidly developing resistance** to **quinolones**.

For more severe MRSA skin and soft tissue infections, telavancin, tigecycline, and ceftaroline are newer options, in addition to vancomycin (still first line), linezolid, and daptomycin. Remember that a MRSA skin abscess (and any abscess for that matter) should be drained whenever possible.

### *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*

*S. epidermidis* and *S. saprophyticus* are examples of coagulase-**negative** staph. *S. epidermidis* is almost always methicillin-resistant. It is the **most common cause** of **both** catheter-related bacteremia (catheter gets contaminated as it passes through the skin) and bacteremia occurring post-op when anything foreign was left in the body (e.g., prosthetics, including heart valves and joints, pacemakers, shunts). Treat with vancomycin +/- rifampin +/- gentamicin. *S. saprophyticus* causes UTIs in young women.

### *Streptococcus pneumoniae*

#### Splenectomy and *S. pneumoniae*

Remember: You need a functioning spleen **and** an ability to make antibodies to defend against encapsulated *S. pneumoniae* and *H. influenzae*—so **both** infections are seen more often in splenectomized patients (including those with sickle cell [SS] disease), very young and old patients, and in CLL, MM, and agammaglobulinemia. Alcoholics also are more susceptible, but **not** because of antibody problems.

Postsplenectomy pneumococcal sepsis can be rapidly fatal and can present with flu-like symptoms, purpura, and DIC. Howell-Jolly bodies, indicative of an asplenic state, are often seen on peripheral smear.

Resistance to penicillin is a problem in *S. pneumoniae* isolates. Around 5% of isolates are defined as “resistant” to PCN (PCN MIC  $\geq 8$  mcg/mL;  $\leq 2$  = susceptible).

### Pneumococcal Pneumonia

Even resistant isolates are not as big a deal if they are in the lungs because most beta-lactams achieve a high concentration in the lungs. Treat susceptible pneumonia with PCN or a 3<sup>rd</sup> generation cephalosporin.



## Quick Quiz

- What is the clinical presentation of toxic shock syndrome?
- How do blood culture results differ between staph and strep toxic shock?
- What is the drug of choice for initial treatment of MRSA bacteremia (until MIC results are available)?
- MRSA treatment failure is associated with organisms with what MIC?
- What other antibiotics are useful to treat skin and soft tissue staph infections?
- What are the drugs of choice for treatment of PCN-susceptible pneumococci?
- What is the treatment of choice for empiric coverage of bacterial meningitis?
- What clinical findings are associated with true streptococcal pharyngitis?

PCN-resistant pneumonia can be treated with a 3<sup>rd</sup> generation cephalosporin, respiratory quinolone (levo-, gemo-, or moxifloxacin), vancomycin, or linezolid. See specifics under Community-Acquired Pneumonia in the Pulmonary Medicine section, Book 2.

### Pneumococcal Meningitis

Empiric treatment for community-acquired meningitis should include vancomycin + 3<sup>rd</sup> generation cephalosporin to account for any beta-lactam resistance.

Focused treatment for susceptible pneumococcal isolates should be with increased doses of ceftriaxone or cefotaxime. Resistant isolates should be treated with vancomycin.

### *Streptococcus pyogenes* (Group A)

*S. pyogenes* is the **only** species in group A beta-hemolytic strep. It may cause **pharyngitis** (Image 2-3), **TSS**, rheumatic fever, **erysipelas** (Image 2-4), or scarlet fever. A cell surface protein, called the “**M protein**,” defines which strains are rheumatogenic, glomerulonephritic, and toxigenic.



Image 2-3: Streptococcal pharyngitis



Image 2-4: Erysipelas

Courtesy: CDC Dr. Thomas F. Sellers, Emory University

Strep pharyngitis (usually *S. pyogenes*) is more likely with each of these 3 findings:

- 1) Temp > 100° F
- 2) Tender cervical lymphadenopathy
- 3) Exudative tonsils

If none of these is present, the chance that pharyngitis is due to strep is < 3%; 1 = 20%; 3 = 50%. On the other hand, if a person comes in with tonsillitis, swollen cervical nodes, and fever but a negative strep test, do you treat with antibiotics? No! What else gives you these symptoms? Think upper respiratory viruses, mononucleosis—and don't forget acute HIV infection (page 2-48)! In adults, if you suspect strep, just do a rapid strep test; do not do a strep culture. Again: With strep TSS, blood cultures are usually positive, whereas with staph TSS, blood cultures are usually negative.

### *Streptococcus agalactiae* (Group B)

*S. agalactiae* (group B) is seen in the very young and very old, **especially** if the elderly patients are alcoholic or diabetic. It is a **major** cause of **newborn pneumonia** and **meningitis**. In pregnant women, *S. agalactiae* causes UTIs and is also a cause of postpartum endometritis and bacteremia. It can originate from a GU reservoir.

Treat with PCN or ampicillin.

### Group D Streptococci

Group D streptococci are inhabitants of the GI tract and are causes of bacteremia and endocarditis. *S. bovis* bacteremia is associated with colon neoplasm in 20–30% of cases.

### Enterococci

Enterococci are gram-positive cocci that are difficult to distinguish from streptococci under the microscope. Similar to streptococci, they occur in pairs and short chains. Two species normally inhabit the intestines with a higher amount of *Enterococcus faecalis* (95%) than *Enterococcus faecium* (5%). Similarly, *E. faecalis* causes the vast majority of enterococcal infections (e.g., UTIs, bacteremia, endocarditis, meningitis, and diverticulitis).

Suspect an enterococcal infection when a patient gets endocarditis or becomes septic after genitourinary manipulation.

**All** enterococci are resistant to cephalosporins and penicillinase-resistant penicillins. They are moderately resistant to the aminoglycosides.

*E. faecium* is one of the few organisms resistant to imipenem and is causing great problems with rapidly emerging, strong resistance to vancomycin (vancomycin-resistant *Enterococcus*, or **VRE**). The incidence of VRE is dependent on the local setting and the use of other antibiotics in the population being treated. Always know the

local antibiogram where you are practicing. VRE tends to be found in liquid tumors and stem cell recipients.

You can treat enterococci with either single drugs or a combination. Single agents used to treat mild-to-moderate infections include PCN G, ampicillin, or vancomycin.

Combination treatment is generally used in *Enterococcus* bacteremia (e.g., sepsis, endocarditis). In these cases, check the isolate for gentamicin susceptibility. If susceptible, add low-dose gentamicin to either PCN G, ampicillin, or vancomycin. The gentamicin adds a synergistic effect because the single drugs are only inhibitory against enterococci whereas gentamicin adds a bactericidal effect.

Review treatment of enterococcal infections:

- Simple enterococcal infections = PCN G, ampicillin, or vancomycin (depending on resistance testing).
- Bacteremia (sepsis or endocarditis) = PCN G or ampicillin or vancomycin + low-dose gentamicin (if susceptible).

### Listeria

*Listeria monocytogenes*, an anaerobic GNR, causes listeriosis, which is associated with decreased **cellular** immunity syndromes such as AIDS, lymphoma, and leukemia. Also, these infections are associated with drugs that depress cellular immunity (glucocorticoids, post-transplant drugs). Listeriosis is also seen in **neonates**, the **elderly**, and **pregnant** women. For some reason, it is not actually seen as much as expected in AIDS patients.

*Listeria* is one of the most virulent foodborne pathogens, and the mortality rate is high. It may be found in deli meats, hot dogs, milk, soft cheeses, poultry, and even fruit. In 2011, an outbreak of *Listeria* in cantaloupe from Colorado resulted in 30 deaths.

*Listeria* can cause neonatal meningitis via transvaginal inoculation and also can affect the fetus. For this reason, pregnant women are cautioned against eating soft cheeses, unpasteurized milk, etc.

Like *Enterococcus*, *Listeria* is resistant to all cephalosporins, which is why you always include **ampicillin** in the empiric treatment for meningitis in the elderly or neonates. Treat mild-to-moderate cases of listeriosis with PCN or ampicillin—with vancomycin or TMP/SMX if allergic to PCN.

Also, as with *Enterococcus*, add an aminoglycoside to the PCN or ampicillin for resistant or serious cases.

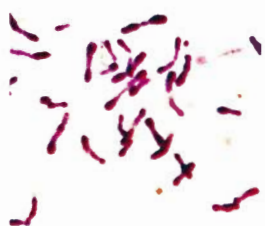


Image 2-5: *C. diphtheriae*



Image 2-6: Pharyngeal membrane

Because aminoglycosides penetrate the CSF poorly, use very **high-dose** PCN or ampicillin to treat listerial meningitis.

Review:

- Mild-to-moderate listeriosis: ampicillin
- Serious/resistant: amp + gentamicin
- Listerial meningitis: high-dose amp +/- gentamicin

### *Corynebacterium diphtheriae*, JK, and *Arcanobacterium haemolyticum*

*Corynebacterium diphtheriae* causes **diphtheria** (Image 2-5). Diphtheria is an upper respiratory infection with a gray-white **pharyngeal membrane** (Image 2-6), hoarseness, sore throat, and a **low** fever (< 101° F). Low fever! Toxic effects include myocarditis with possible cardiac failure and polyneuritis. Treatment is erythromycin. Second choice is penicillin. Diphtheria antitoxin is **always** given with the antibiotic.

*Corynebacterium jeikeium* (JK) is especially problematic in **neutropenic** patients and in **bone marrow transplant** units, where it is a cause of IV catheter-related infections. It is resistant to most drugs. Vancomycin is the drug of choice.

*Arcanobacterium haemolyticum* causes **pharyngitis** in adolescents, similar to that of *S. pyogenes*, with a desquamative scarlatiniform rash and lymphadenitis. Treat with PCN, erythromycin, or tetracycline.

### *Bacillus anthracis* and *Bacillus cereus*

*Bacillus anthracis* are large, gram-positive rods that cause **anthrax**.

There are 3 main clinical manifestations:

- 1) Cutaneous (95%)
- 2) Pulmonic ("wool sorter's disease")
- 3) Pharyngeal + gastrointestinal

Inoculation occurs from handling naturally contaminated hides/wool or, more recently, maliciously contaminated sources (e.g., mail or food). Virulence requires a 3-component protein exotoxin. The component proteins are edema factor (causes edema), lethal factor (causes death!), and "protective antigen."

Anthrax is **not** transmitted person to person.

**Cutaneous** anthrax starts as a **painless** papule that vesiculates and forms a **painless** ulcer (Image 2-7), then a **painless** black eschar, often with a lot of nonpitting, **painless** induration (Image 2-8).

**Inhalation** anthrax presents similarly to influenza with malaise, fever, and myalgias. After 2–3 days, there is a dramatic worsening of symptoms with hypoxia, and then hypotension and death. An important diagnostic finding with inhalation anthrax is **mediastinal widening**.



## Quick Quiz

- When should you use 2 antibiotics to treat enterococcal infections? Which drugs would you choose?
- Which patient populations are at risk for *Listeria*?
- Treatment of serious *Listeria* infections includes which drugs?
- What are the clinical manifestations of anthrax?
- Inhalation anthrax is associated with what important physical finding?
- What is the timing of vomiting due to *B. cereus* toxin ingestion?
- What is the clinical presentation of meningococcemia? Empiric treatment?

**Gastrointestinal anthrax** is acquired by eating undercooked, contaminated meat. Patients get pharyngeal eschars and/or severe GI distress.

Anthrax is usually sensitive to penicillin, tetracycline, erythromycin, and quinolones. The 2001 anthrax bioterrorism infections in the U.S. had an inducible beta-lactamase, which led to the recommendation of quinolones for treatment and prophylaxis.

*Bacillus cereus* is a close relative of *Bacillus anthracis*. Emetic toxin and enterotoxin-producing strains cause gastroenteritis of 2 varieties:

- 1) A short incubation (1–6 hr) **emetic** type
- 2) A longer incubation (8–16 hr) **diarrheal** type

The emetic form is associated with **fried rice** not cooked at a high enough temperature (not good) and then left too long at room temperature (even worse; allows the spores to germinate). As with *S. aureus*, the emetic toxin is produced outside the host, is preformed in foods, and therefore provokes a rapid onset of symptoms (1–6 hr). This gastroenteritis is self-limited and necessitates only **symptomatic** treatment.

The **diarrheal** form can be from preformed enterotoxins or toxin produced *in vivo* after ingestion of the bacilli. It results in a profuse, watery, non-bloody diarrhea, accompanied by abdominal pain and cramps, nausea and

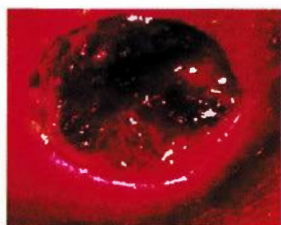


Image 2-7: Anthrax ulcer (painless)

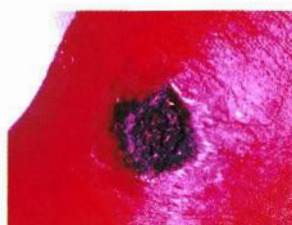


Image 2-8: Cutaneous anthrax lesion

Courtesy: CTR James H. Steele

occasionally vomiting. The incubation period is 8–16 hours, and it resembles *C. perfringens* food poisoning. Symptoms usually resolve in 12–24 hours. No specific therapy is necessary.

*B. cereus* is an occasional cause of infection in contact lens wearers, after a traumatic eye injury, and is a possible cause of IV catheter-related infections. Treatment for serious disease is vancomycin.

## Clostridium

*Clostridium* is a strict anaerobic gram-positive rod:

- *C. difficile* causes antibiotic-associated colitis. (See [page 2-59](#).)
- *C. botulinum* causes botulism—this toxin is the most potent known! It blocks presynaptic acetylcholine release.
- *C. perfringens* is one of the most common causes of food poisoning in the U.S. and presents as a 24-hour (or less) diarrheal illness. It is associated with contaminated meat or gravy.
- *C. septicum*: The majority of patients with *C. septicum* **sepsis** have an associated GI malignancy.
- *C. tetani* is the cause of tetanus.

Cellulitis and gas gangrene can be caused by *C. septicum*, *perfringens*, *tetani*, or *novyi*. The main toxin in all *Clostridia* is the **alpha toxin**. For acute treatment of *C. tetani* infection, use **antitoxin** plus **metronidazole** (now the antibiotic of choice instead of PCN, which is still an alternative). For tetanus, also remember to give tetanus toxoid and immune globulin ([page 2-66](#)).

## GRAM-NEGATIVE BACTERIA

### Neisseria

*Neisseria meningitidis* (meningococcus) is a **gram-negative coccus** that is an occasional, ordinary inhabitant of the human throat. It usually does not cause disease because specific antibodies (humoral defense) and complement lyse the organisms as they enter the bloodstream.

Patients with complement deficiency are especially prone to **meningococcemia**, which presents with fever, hypotension, and skin signs that vary from petechiae (early disease) to diffuse purpuric lesions (later). DIC.

Treat patients with suspected infection empirically with a 3<sup>rd</sup> generation cephalosporin (+ vancomycin if meningitis) until susceptibilities are known. Once known, treat meningococcemia and meningitis due to PCN-susceptible isolates with penicillin. Keep the 3<sup>rd</sup> generation cephalosporin if there is any PCN resistance. Use chloramphenicol in patients with severe PCN allergy. With prompt treatment, the mortality rate of meningococcemia is 10%.

[Know:] **Prophylaxis** should be given to certain contacts of patients with meningococcal bacteremia and meningitis to eradicate colonization of the anterior nasopharynx, which has been associated with subsequent development of invasive disease. [Definitely know:] Give prophylaxis only to “close contacts” of infected patients.

Close contacts are defined as:

- People who live in the patient’s household
- Contacts at day care
- People exposed to the patient’s oral secretions (Usually this is a health care worker who has intubated the patient. Know that the traditional clinical encounter does **not** merit prophylaxis for health care workers because traditional encounters usually do not involve contact with the patient’s oral secretions.)

To eradicate the carrier state use:

- rifampin (children and non-pregnant adults),
- fluoroquinolones (non-pregnant adults), or
- ceftriaxone (pregnancy and children < 15 years of age).

[Know:] Patients with meningococcal disease who are treated with penicillin still need to be given one of these “prophylaxis” drugs, because the penicillin does not eradicate organisms from the anterior nares.

*Neisseria gonorrhoeae* causes gonorrhea and bacteremia. It is a gram-negative organism, usually seen as diplococci. The penicillinase-producing strains of *N. gonorrhoeae* now account for the majority of cases in many areas in Asia and Africa and are also common in the U.S. More in the discussion on STDs (page 2-59).

### Moraxella

*Moraxella catarrhalis* is a **gram-negative coccus** that causes respiratory infections, especially in immunodeficient patients and those with COPD. It is a common cause of **sinusitis** in adults and **otitis media** in children. Treat adults with amoxicillin-clavulanate, a 2<sup>nd</sup> or 3<sup>rd</sup> generation cephalosporin, or a quinolone. In the U.S., almost all are susceptible to erythromycin, tetracycline, and TMP/SMX.

### Pseudomonas

*Pseudomonas aeruginosa* is a **gram-negative rod** with a single flagellum. Suspect *Pseudomonas aeruginosa* if there is a history of **nail-puncture** wounds, especially if through a tennis shoe; osteomyelitis and endocarditis in injection drug users; and acute or chronic otitis externa, which can be especially severe in diabetics.

**Ecthyma gangrenosum**—a round, indurated **black** lesion with central ulceration—may accompany pseudomonal bacteremia.

*Pseudomonas* is the cause of “hot tub rash,” which people get from improperly chlorinated hot tubs; this is usually self-limited.

Treat serious infections with 2 antipseudomonal drugs until you know the susceptibility of the isolate, because these GNRs tend to be resistant. Effective drugs include:

- Ciprofloxacin
- Aminoglycosides
- ES-PCN + BLI
- Carbapenems
- Aztreonam
- Cefepime
- Ceftazidime

### Enterobacteriaceae

*Enterobacteriaceae* is a family of gram-negative enteric bacilli (GNRs) that includes: *Salmonella*, *Yersinia*, *Shigella*, *Citrobacter*, *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Enterobacter*, and *Edwardsiella*. We’ll discuss *Salmonella* and *Yersinia* now.

### Salmonella

*Salmonella* are **gram-negative bacilli** that are usually motile.

Non-typhoidal *Salmonella* are a fairly common cause of diarrhea. Because the bacteria are not host-adapted, like *S. typhi*, they can be found in many different, non-human host animals. *Salmonella* may be spread by frozen foods (especially chicken), milk, and eggs. **Peanut butter** and **alfalfa sprouts** were recent sources of outbreaks. Baby chicks, **iguanas**, turtles, and other exotic pets may also be sources of infections. Treatment is usually symptomatic only because antibiotic therapy increases the risk of developing a carrier state.

*Salmonella typhi*, unlike most *Salmonella*, is non-motile and encapsulated. It causes **typhoid fever**, usually from contaminated food, milk, or water. **Adults** are more likely to be carriers because *S. typhi* tends to seed in **gallstones**. The infection is associated with leukopenia and the appearance of classic “**rose spots**” (Image 2-9) on the trunk, which begin about a **week** after the fever starts. These look like little 2–3 mm diameter angiomas.

Recommend typhoid **vaccine** to travelers (> 2 years old) who go outside of the usual tourist areas of Latin America, Asia, and Africa.

Treatment of typhoid fever: Options include quinolones, 3<sup>rd</sup> generation cephalosporins, ampicillin, TMP/SMX, and chloramphenicol, depending on sensitivities. Carriers without gallbladder disease or stones can usually



Image 2-9: Typhoid fever with classic “rose spots”

Courtesy: CDC, Armed Forces Institute of Pathology  
Charles N. Farmer



## Quick Quiz

- Prophylaxis for meningococemia should be given to which contacts?
- When should you suspect *Pseudomonas* as a cause of infection?
- *Salmonella* infection is spread by which animals?
- Which form of plague is transmitted person-to-person?
- What associated symptoms are often observed with *Legionella* pneumonia?
- Which geographic locations have the most cases of tularemia?

be cleared with 6 weeks of ampicillin + probenecid. The probenecid decreases clearance and causes a higher blood level of the ampicillin.

### *Yersinia*

*Yersinia pestis* is a **gram-negative coccobacillus** that causes **plague**. Reservoir is wild rodents. It is transmitted by fleas or direct contact (skinning animals) and has a high mortality.

The **bubonic** type causes large, localized lymphadenopathy (“buboes”) that suppurates. If not treated, it can lead to sepsis and death. The bubonic type also may lead to a **pneumonic** form, which is rapidly transmitted to bystanders by coughing.

Plague and tularemia present similarly (adenopathy after hunting), except that the geographic locations are different—desert Southwest for plague vs. Arkansas, Missouri, and Oklahoma for tularemia. More on tularemia below.

Diagnose plague by aspirating the lymph nodes.

Treat plague with streptomycin. 2<sup>nd</sup> line choices are tetracycline or quinolones.

Other *Enterobacteriaceae* are covered in the Diarrhea topic in the Gastroenterology section, Book 1.

### *Legionella*

The *Legionellaceae* family is made up of many species. *Legionella pneumophila* causes 80–90% of human *Legionellaceae* infections. *Legionella* are **aerobic gram-negative bacilli** that require special media for culture (charcoal yeast extract). *Legionella* are contained in water, and modes of transmission are multiple—with **aspiration** being the most likely.

*Legionella pneumophila* infection (legionellosis) causes **legions** of problems. Multisystem disease is the clue! Patients often present with **diarrhea** and CNS

symptoms (H/A, delirium, and **confusion**), in addition to the pneumonia. Treatment for moderate infections is **azithromycin** or **quinolones**. If severely ill, add rifampin.

### *Brucella*

*Brucella* is an aerobic **gram-negative** bacillus, and *B. melitensis* causes brucellosis in goats, sheep, and camels. Other strains: *Brucella abortus* (cattle), *B. suis* (pigs), and *B. canis* (dogs). These are often transmitted to humans via unpasteurized milk or cheese or by inhalation (work-related). *Brucella* affects the:

- heart (especially suspect in **culture-negative** endocarditis),
- lungs,
- GI tract,
- GU area (orchitis, abortion), and
- endocrine glands (thyroiditis, adrenal insufficiency, SIADH).

Confirming the diagnosis is difficult because cultures may take up to 6 weeks to grow. You can also check acute and convalescent serum titers.

Treatment requires 1 of the following regimens:

- Doxycycline + aminoglycoside (streptomycin or gentamicin) x 4 weeks
- Doxycycline + rifampin x 4–8 weeks

### *Francisella*

*Francisella tularensis* is a small, **gram-negative pleomorphic bacillus** that causes **tularemia** (“rabbit fever”). It is found in many animals. It is transmitted by ticks and bloodsucking flies, but the organism may also be ingested or inhaled. Especially seen in **Arkansas, Missouri, and Oklahoma**.

Typically, patients with tularemia present with a history of sudden onset of fever, chills, myalgias, and arthralgias, followed by an irregular ulcer at the site of inoculation that may persist for months. Regional **lymphadenopathy** develops, and these nodes may necrose and suppurate.

Base the diagnosis of tularemia on the typical clinical presentation and serologic testing for *Francisella tularensis*. Differential includes **plague**, which occurs mostly in the **desert Southwest**.

Treat with streptomycin or gentamicin. Tetracycline can be used if the patient is not severely ill.

### *Bartonella*

*Bartonella henselae* causes **cat-scratch disease** or, in the immunocompromised patient, **bacillary angiomatosis**. The skin lesions of bacillary angiomatosis are identical to verruga peruana (next). See **Image 2-10**.

Treatment for bacillary angiomatosis: erythromycin or doxycycline. Data support treating cat-scratch lymphadenitis with azithromycin.



Image 2-10: Cat-scratch disease, primary lesion

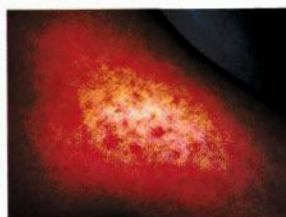


Image 2-11: Rocky Mountain spotted fever

*Bartonella bacilliformis* are tiny, gram-negative pleomorphic bacteria that cause bartonellosis. *Bartonella* is transmitted by sand flies only in Peru, Columbia, and Ecuador and only in certain areas of the Andes Mountains—called the “verruca zone.” Rare outbreaks where there are no sand flies indicate other vectors can exist. The only known reservoir is humans.

Bartonellosis has 2 manifestations:

- 1) Oroya fever (or Carrión disease) (acute/severe)
- 2) Verruga peruana (chronic)

Oroya fever consists of a rapid, febrile hemolytic anemia with a high mortality if untreated (~ 50%)! Superinfection is a common problem—usually with *Salmonella*, staph, or *Enterobacter*. Suspect this disease in acutely ill travelers to the “verruca zone.”

Verruga peruana presents 2–8 weeks after Oroya fever or inoculation. (Up to 50% have no memory of a febrile illness.) It presents with growths of hemangioma-like tissue progressing from pinpoints (miliary), to nodules, to larger (mular) lesions. All stages can exist in the same person.

The drugs of choice for Oroya fever are chloramphenicol plus penicillin. Rifampin is the drug of choice for verruga peruana.

### ***Helicobacter pylori***

*Helicobacter pylori* is a gram-negative, spiral, flagellated bacillus. It causes gastritis and PUD and is a risk factor for adenocarcinoma of the stomach. Further discussion about *H. pylori* is in the Gastroenterology section, Book 1.

## **RICKETTSIA**

### **Rocky Mountain Spotted Fever**

*Rickettsia rickettsii* is a gram-negative coccobacillus that causes Rocky Mountain spotted fever (RMSF). This disease has a 3% overall mortality, but the rate is higher in the elderly (4–9%). Classic signs and symptoms include a rash, fever, headache, arthralgias (but not overt arthritis), and a history of recent exposure to ticks. The rash occurs on the distal extremities (Image 2-11). It progresses from maculopapular to petechial. Most infected persons get the rash, but few get all of the classic signs and symptoms. Patients may also present with diarrhea and abdominal pain.

Labs may show leukopenia or leukocytosis, thrombocytopenia, hyponatremia, and increased transaminases. PT, PTT, and fibrin split products are often increased, although the condition is not often associated with true DIC. The increase in these parameters is thought to be due to organism-induced local injury in the blood vessels.

Most clinicians diagnose this on clinical grounds, start treatment, and then confirm with serological testing. For a definite diagnosis, do immunofluorescent staining on a biopsy of the petechial lesion. Treat with tetracycline/doxycycline or chloramphenicol.

Other rickettsial infections include *R. typhi* (endemic typhus), *R. prowazekii* (epidemic typhus), *R. conorii* (Mediterranean spotted fever), and *Coxiella burnetii* (Q fever).

### **Q Fever**

Know that Q fever, caused by *Coxiella burnetii*, is a zoonosis that is transmitted to humans mainly by inhalation of the aerosol released from the infected animal. Q fever is seen in abattoir (slaughterhouse) workers and people exposed to an infected animal's products of conception during birthing.

Treat symptomatic Q fever with doxycycline. Commonly the disease remits spontaneously. Occasionally, chronic Q fever may present as a fever of unknown origin, and/or culture-negative endocarditis. Diagnose with serology.

### ***Ehrlichia***

*Ehrlichia* are small, obligately intracellular gram-negative organisms that cause ehrlichiosis. Ehrlichiosis has been called “spotless Rocky Mountain fever.” Like RMSF, ticks are the transmission vector.

There are 2 forms of ehrlichiosis caused by two types of *Ehrlichia*:

- 1) Human monocytic ehrlichiosis (HME)
- 2) Human granulocytic anaplasmosis (HGA)

HME is due to *E. chaffeensis* and mainly seen in Missouri and Arkansas.

HGA is due to *Anaplasma phagocytophilum* and predominates in the Northeast and upper Midwest U.S.

There is usually no rash. The organism affects the monocytes or neutrophils, and patients typically present with the viral picture of fever, headache, and leukopenia—they may also have thrombocytopenia. Think of this in the patient who presents with pancytopenia and history of tick bite.

Treat all patients suspected of having ehrlichiosis or anaplasmosis. Treatment is doxycycline/tetracycline. History and lab are similar to RMSF, so it is commonly confused with it. Fortunately the treatment is the same for both!



## Quick Quiz

- What are the manifestations of bartonellosis?
- Name the clinical signs and symptoms of RMSF. What drugs are used for treatment?
- What is Q fever? How is it treated?
- What are the forms of ehrlichiosis? How does it present?
- *M. marinum* causes what type of infection?
- If a pathology report describes beaded, branching, mildly acid-fast, filamentous organisms, what organism is likely?
- What organism is associated with an IUD?

Note: There are reports of dual infection with *Ehrlichia* + *Babesia microti* (an intraRBC protozoan parasite) and *Ehrlichia* + *Borrelia burgdorferi* (Lyme) in the endemic Northeast areas.

## GRAM-VARIABLE BACTERIA

*Gardnerella vaginalis* is a gram-variable rod. It is one of the bacteria associated with bacterial vaginosis, the most common cause of vaginal discharge in women of child-bearing age. Treat with metronidazole or tinidazole.

## ACID-FAST BACTERIA

### Mycobacteria

All mycobacteria are acidfast bacteria (red on a green background).

*M. tuberculosis* can cause pleural effusions with a lymphocyte count of 1,000–6,000/mm<sup>3</sup>, a low glucose, elevated protein, and elevated LDH. The glucose is normally > 80, although, in 20% of cases, it is < 60. More on TB in the Pulmonary Medicine section, Book 2.

*M. avium intracellulare* complex or *M. avium* complex (MAI or MAC) is a chronic pulmonary infection caused by either *M. avium* or *M. intracellulare*. It typically occurs in immunocompromised (especially HIV) patients and requires prolonged multi-drug treatment.

*M. scrofulaceum* and MAC cause lymphadenitis in children; treat by excising the nodes.

“Nontuberculous mycobacteria” (NTM) usually refers to MAC, *M. kansasii*, and *M. abscessus*, which cause chronic pulmonary infections. These infections require prolonged multi-drug treatment.

*M. leprae* causes leprosy. Transmission is probably via respiratory droplets person-to-person. Diagnose with Fite stains of skin or nerve. Armadillos also may carry *M. leprae* and are a reservoir in the southern U.S.

*M. marinum* is the “fish-tank bacillus.” It causes non-healing skin ulceration in people working around fish tanks (especially if any immunodeficiency is present, such as diabetes). It often causes strings of lesions along the lymphatic channels. (Similar lymphatic channel lesions occur with *Nocardia brasiliensis* and *Sporothrix schenckii*.) Treat *M. marinum* with clarithromycin + either rifampin or ethambutol until 1–2 months after symptoms resolve.

### Nocardia

*Nocardia asteroides* is only weakly acidfast (easily missed). Its shape is beaded, branching, and filamentous. It usually starts as a lung infection—occasionally causing a thin-walled cavitary lesion. It can cause focal brain abscesses and a chronic neutrophilic meningitis—most chronic meningitides are lymphocytic. Nodular skin lesions are common. It is hard to isolate.

Usual treatment is high-dose sulfonamides or TMP/SMX. In severely ill patients, add combinations of drugs including amikacin + imipenem. Minocycline is another alternate choice for those sulfa-allergic.

*Nocardia brasiliensis* is in the soil. Like *M. marinum* and *Sporothrix schenckii*, it can cause inflammation with associated surface lesions along lymphatic channels. Treat with sulfonamides or TMP/SMX. *Nocardia brasiliensis* is resistant to imipenem, but *N. asteroides* is sensitive.

## OTHER ORGANISMS

### Actinomyces

*Actinomyces* is an anaerobic organism that causes an infection in which yellow “sulfur” granules can be visualized, which are actually clusters of organisms. The usual presentation of actinomycosis is cervicofacial involvement (“lumpy jaw” Image 2-12). *Actinomyces* is a cause of PID when there is an IUD in place. Also, in the abdomen, be aware of *Actinomyces* associated with appendicitis. Treatment is PCN or ampicillin; 2<sup>nd</sup> choice is tetracycline.



Image 2-12. Actinomycosis

### Chlamydia / Chlamydophila

*Chlamydia* and *Chlamydophila* are obligate, intracellular parasites. *C. psittaci*, *C. trachomatis*, and *C. pneumoniae* (formerly TWAR) are pathogenic in humans. Treat with doxycycline, macrolides, or quinolones.

*C. psittaci* is found in psittacine and other birds and causes psittacosis: pneumonia and **splenomegaly**. Again: Any pneumonia associated with poultry, especially with splenomegaly, strongly suggests *C. psittaci*. (DDx: *Histoplasma* also causes pneumonia and splenomegaly; it is associated with bird and bat droppings.) Onset of psittacosis is associated with myalgias, rigors, headache, and high fever—to 105° F.

*Chlamydophila pneumoniae* causes community-acquired pneumonia in adults who typically have **not** been exposed to birds; i.e., person-to-person spread. Bronchospasm is particularly prominent in respiratory infection caused by *C. pneumoniae*, as is an association with early pharyngitis and hoarseness.

*Chlamydia trachomatis* causes GU infections and **trachoma** (chronic, **external** eye infection causing cataracts but **not** glaucoma; found especially in Asia and Africa). Approximately 5% of pregnant women have *C. trachomatis* in their genital tracts. The same *C. trachomatis* is also associated with **neonatal** pneumonia! Lymphogranuloma venereum is a STD caused by the same *C. trachomatis*, but a different immunotype.

## SPIROCHETES

### SYPHILIS

*Treponema pallidum* causes syphilis. Sequence of infection:

- **Primary** syphilis presents with a painless chancre (genital, anal, or oral) within 3–40 days, depending on the number of inoculating organisms, and **regional** lymphadenopathy. In women, if the infection is **cervical**, it is often **asymptomatic**. Chancre lasts 2–6 weeks, then resolves.
- **Secondary** syphilis occurs ~ 2 months later with generalized lymphadenopathy, constitutional symptoms, and mucosal and/or cutaneous lesions that can mimic many other lesions (“the great imitator”). The skin lesions may be macular or papular but are rarely vesicular. They can occur on the palms and soles and are described as “nickel and dime” lesions (Image 2-13). Meningovascular disease can also occur in secondary syphilis (strokes). These signs and symptoms resolve in 3–12 weeks, and the disease goes into a **latency period**. Untreated, 1/3 of secondary syphilis cases eventually proceed to **tertiary** syphilis.
- **Tertiary** syphilis occurs 1–10 years or more after the initial untreated infection. It causes gummas, which are soft granulomas. Gummas in turn cause a chronic inflammatory state. Tertiary syphilis also can cause aortitis and CNS disease. Neurosyphilis can present as tabes dorsalis (foot-slap and widebased gait) or

general paresis. A nice mnemonic for the cognitive impairments seen in tertiary syphilis:

- P = defects in **personality**
- A = reduced **affect**
- R = abnormal reflexes
- E = **eyes** (Argyll-Robertson pupil, which is miotic and irregular; constricts normally to accommodation but not to light)
- S = defect in **sensorium**
- I = defect in **intellect**
- S = defect in **speech**

Darkfield microscopy of exudate or tissue of a chancre is diagnostic but rarely available. Today, diagnosis of syphilis is done with serologic tests. There are 2 general types of serologic tests:

1) Non-treponemal/reagin (VDRL and RPR)

2) Treponemal (MHA-TP and FTA-ABS)

By either type of test, 20–30% of patients with primary syphilis are negative but will turn positive shortly thereafter. By either test, 99–100% of patients will be positive in secondary and tertiary syphilis.

Screen with VDRL or RPR and if that is positive; then do a specific test (MHA-TP or FTA-ABS). (Some state labs do this backwards [for cost reasons] and do a different specific syphilis ELISA test first; this is controversial and many experts do not think this is best [extremely high rate of false positives].)

Once positive, the specific treponemal tests (MHA-TP and FTA-ABS) usually stay positive for life. The non-treponemal tests become negative after treatment unless treatment has been delayed for many years, in which case they may stay positive.

Scenarios:

- **+RPR, –MHA-TP** = one of following:
  - Early infection.
  - False positive in low-risk population. Repeat in 6 weeks.
- **+RPR, +MHA-TP** = infection.
- **–RPR, +MHA-TP** = longstanding untreated tertiary disease or a false positive due to cross-reacting antibodies from Lyme infection.



Image 2-13: Secondary syphilis “nickel and dime” lesions

Courtesy: CLIX



## Quick Quiz

- What associated symptoms are often seen in respiratory infections due to *C. pneumoniae*?
- Stroke may occur in which stage of syphilis?
- What does PARESIS stand for, when referring to tertiary syphilis?
- When will an MHA-TP revert to negative after a patient has syphilis?
- Can a patient have a negative RPR and have neurosyphilis?
- List the treatment regimens for the various stages of syphilis.
- What drug is used to treat syphilis in pregnancy? What if the woman has an anaphylactic PCN allergy?
- What is the clinical presentation of leptospirosis?

Antibodies to *Borrelia burgdorferi* (Lyme's) cross-react and may cause a false-positive treponemal test (MHA-TP and FTA-ABS), but these antibodies do not affect a nontreponemal test (VDRL and RPR).

If the VDRL or RPR becomes negative **after** treatment, it is a good indication of successful treatment. These nontreponemal tests may also become negative in **untreated** persons with tertiary syphilis. So, secondary syphilis can typically be screened out by either test being negative; only the treponemal test can be used to screen out tertiary syphilis. Notice this does not say "rule out" because, unfortunately, the false-negative rate in tertiary syphilis with the reagin (non-treponemal; VDRL and RPR) tests is up to 30%!

All **pregnant** women should get a **non-treponemal** test in the 1<sup>st</sup> trimester. If at high risk, repeat in the 3<sup>rd</sup> trimester and at delivery.

Note: All of the standard antibody tests in a newborn are positive if the mother was positive—because of cross-over of IgG. The previously used newborn IgM test was not very sensitive because the maternal IgG tended to "overwhelm" IgM response.

Treatment of syphilis:

For **primary syphilis** and for the **early latency period** of secondary syphilis (< 1 year since acquiring the disease):

- Benzathine PCN G 2.4 MU IM or doxycycline 100 mg bid x 14 days

For **late latency** secondary syphilis and **tertiary** syphilis with gummas or cardiovascular problems:

- Benzathine PCN G 2.4 MU IM q week x 3 or doxycycline 100 mg PO bid x 4 weeks

For **neurosyphilis**:

- PCN G 18–24 MU IV divided q 4 hours or continuous infusion for 10–14 days. This is sometimes followed by benzathine PCN 2.4 MU IM q wk x 3. An alternative is procaine PCN 2.4 MU IM qd with probenecid 500 mg qid x 14 days. If PCN-allergic, the best course is to desensitize the patient and give the PCN. Use ceftriaxone as an alternative for PCN-allergic patients with 2 grams a day x 10–14 days. Oral doxycycline is **not** effective for neurosyphilis.

Treat pregnant women and newborns for syphilis only with PCN. If the pregnant woman is **PCN-allergic**, **desensitize** her (see [page 2-10](#)), then treat with PCN. After treatment, do a quantitative **nontreponemal**/reagin test monthly during pregnancy.

## LEPTOSPIROSIS

Leptospirosis is a spirochetal disease caused by *Leptospira interrogans* and transferred by **contact** with infected animals or contaminated water. Leptospirosis is considered to be the most widespread zoonosis in the world. It is common in **Hawaii** (~ 50% of all U.S. cases) and may be seen in cross-country runners, white water rafters, and triathletes—usually after contamination has been spread by **heavy rains** and **flooding**. Look for contact with **dog** or **rat urine**.

Leptospirosis has a wide range of signs and symptoms, from myalgias, fever, subconjunctival suffusion, headache with or without aseptic meningitis, to **Weil syndrome** (severe hepatitis with renal failure, pneumonitis, and hemorrhagic complications). The hepatitis is characterized by the bilirubin being disproportionately elevated compared to the liver enzymes. The variety of presenting symptoms makes for a high incidence of initial misdiagnoses.

Diagnose with blood and/or CSF cultures on special media within the first 10 days of illness. After that, culture the urine and send serum for anti-leptospiral IgM. Treat with PCN or doxycycline.

## LYME DISEASE

### Overview

*Borrelia burgdorferi* causes **Lyme disease**. It is transmitted by the *Ixodes scapularis* tick in the Northeast and the *Ixodes pacificus* tick in California. Remember: The protozoan *Babesia* is also transmitted by *Ixodes scapularis*—see [page 2-32](#). The *I. scapularis* tick seems to be a better vector, so the disease is most prevalent in the Northeast, especially Martha's Vineyard and the Nantucket area. *Borrelia burgdorferi* **does** cross the **placenta** and causes fetal infection and death.

For the most part, ticks transmit Lyme disease during the nymph stage, probably because nymphs are more likely

to feed on a person and are **rarely noticed** because of their small size ( $< 2$  mm). Thus, the nymphs typically have ample time to feed and transmit the infection. (Ticks are most likely to transmit infection after  $\sim 2$  or more **days** of feeding.) If a patient says he had a tick on his body for 1 or 2 hours the previous day, just reassure him that no treatment is necessary.

### Diagnosis of Lyme Disease

A definite diagnosis may be difficult to establish. Serology is negative in 90% of Stage I, so base the diagnosis on history plus clinical findings.

**Stage I. Erythema migrans (EM)** is the pathognomonic skin lesion of the early Stage I disease; it starts at the site of the bite and is a slowly spreading, irregular erythematous lesion with a clear center (**Image 2-14**). Early symptoms include myalgias, arthralgias, fever, HA, and lymphadenopathy.

**Stage II.** Then, weeks to months later, Stage II disease occurs with recurring erythema migrans (rare), **neurologic** problems (lymphocytic meningitis and/or neuritis), and **heart** problems (myocarditis, which may cause a **rapidly alternating** 1<sup>st</sup>, 2<sup>nd</sup>, or 3<sup>rd</sup> degree AV block). The neuritis often presents as a peripheral neuropathy, a cranial nerve palsy, or both; consider it in a patient with a suggestive history and Bell's palsy, foot drop, or both.



Image 2-14: Erythema migrans

**Stage III.** Months-to-years later, Stage III occurs, most commonly, with **arthritis** (oligo- or migratory—small or large joints—usually large), but there can also be chronic neurologic syndromes.

### Scenarios

Scenario 1: **No** prophylaxis is given for outdoor activities such as hiking and camping.

Scenario 2: If a patient presents with **erythema migrans**, do you want to check Lyme serology? The answer is **no!** Just treat!

Scenario 3: If a patient presents with fatigue, joint stiffness (not arthritis), and muscle aches and/or tenderness, do you suspect Lyme disease? **No!** Do not check Lyme titers and **do not treat** for Lyme based on these **nonspecific** findings!

Scenario 4: For patients with history of outdoor activities or tick bites with an exposure to an endemic area, check

serology. [Know:] There is a high rate of false-positive ELISA tests, so positive tests are confirmed with Western blot.

### Treatment of Lyme Disease

Keep in mind the treatments are different for those with early disease/Bell's palsy vs. arthritis vs. cardiac or neurologic disease:

- Treat **early disease** and **Bell's palsy** with oral doxycycline or amoxicillin  $\times 10$ –21 days.
- Treat isolated Lyme **arthritis** with oral doxycycline or amoxicillin  $\times 28$  days. Incomplete resolution can be treated with the same agent for an additional 28 days. Refractory disease is treated with synovectomy and/or hydroxychloroquine.
- Treat **cardiac** and **neurologic** disease with ceftriaxone 2 gm or PCN G 20 MU IV in divided doses  $\times 21$  days.

There is no role for long-term antibiotic treatment for "chronic Lyme disease."

## FUNGI

### OVERVIEW

Fungi are roughly divided into 2 morphologic types: **yeasts** and **molds**. There is also a **dimorphic** type that changes from a yeast to a mold, and vice versa, depending on temperature. The dimorphs are the type most likely to cause **systemic** disease in the nonhospitalized, immunocompetent host. The dimorphic fungi are also more limited in environment. With dimorphs, the infectious part of the fungus is the spores (molds), which convert to yeasts at body temperature.

Clinically relevant fungi include the following:

- *Candida* species
- *Cryptococcus* species
- *Aspergillus* species
- Endemic fungi (*Histoplasma*, *Blastomyces*, and *Coccidioides*)
- Dermatophytes (cause tinea capitis, tinea corporis, tinea pedis, and tinea cruris)
- *Sporothrix schenckii*
- Zygomycetes (*Mucor*, *Rhizopus*, and *Cunninghamella*)

### CANDIDA

Candidal infections are usually caused by *Candida albicans*. Infections with this organism are more likely to occur in patients:

- who are immunosuppressed,
- on antibiotics (or doing poorly despite antibiotics),
- with indwelling catheters, or
- with **uncontrolled diabetes**.



## Quick Quiz

- What symptoms are associated with the various stages of Lyme disease?
- What is the treatment for Lyme with heart block?
- When can you disregard *Candida* as a blood culture contaminant?
- What is the treatment of candidemia?
- What patient population develops hepatosplenic candidiasis?
- Patients with candidemia should have what kind of referral?

Mucocutaneous candidiasis is occasionally the presenting symptom of diabetes.

Presentations vary. Disease can be localized to:

- Mucosa (thrush [oropharyngeal], esophagitis, or genitourinary infection)
- Bloodstream (candidemia)

However, *Candida* can also cause **invasive diseases** such as endocarditis, ocular disease, hepatosplenic, and renal fungus ball. Usually, candidemia is the source of dissemination to these other organ systems.

Physical exam findings depend on the extent of the infection and the immune status of the patient. Limited mucosal *Candida*, such as thrush, is visible as whitish plaques with an underlying erythematous base. Patients who have esophageal symptoms and thrush can be assumed to have esophageal candidiasis—a scope is not required to make that diagnosis. Vulvovaginal candidiasis is obvious as a thick, whitish discharge in the setting of intense vaginal itching.

### Candidemia

Fever; rash or painless, erythematous pustules; vision complaints; and multiorgan system failure are signs and symptoms of disseminated disease (at minimum, fungemia). *Candida* species **grow readily** in routine blood culture bottles. Know that *Candida* in a blood culture is **never** a contaminant; it represents real disease, even if the patient is relatively asymptomatic. Any localizing signs, such as rash, should be considered for biopsy—sometimes a skin biopsy is the only way to make the diagnosis of disseminated *Candida*. Also, it may take days to grow the organisms out of the blood. If your patient is sick, it is sometimes appropriate to initiate empiric antifungal treatment, depending on the underlying risk for a fungal infection. It takes additional days to determine the species of the organism.

Treatment includes removal of any infected catheters and giving a systemic antifungal. Which antifungal to initiate for empiric treatment is based on whether a patient is **neutropenic** and whether any fungal infection is likely

to include any **fluconazole-resistant** candidal species; e.g., if the patient is already colonized with *C. glabrata* or *C. krusei*.

- Fluconazole or an echinocandin (caspo-, mica-, anidulafungin) are the 1<sup>st</sup> line agents in non-neutropenics. In patients with moderately severe to severe disease, those with recent azole exposure, and in those known to be colonized with azole-resistant species, echinocandins are the 1<sup>st</sup> line.
- In neutropenia, caspofungin (the only FDA-approved echinocandin for this indication) is preferred. Other options include lipid amphotericin B or voriconazole.

### Hepatosplenic Candidiasis

Also called chronic disseminated candidiasis, this entity is virtually always seen in **leukemic** patients as they recover from a period of **neutropenia**. Symptoms include fever and pain in the right upper quadrant.

Labs show increased alkaline phosphatase +/- increased transaminases and bilirubin. A contrasted CT of the abdomen will show small abscesses in the liver and spleen.

Treatment is usually lipid amphotericin B (because it must be given for a long time) x 14 days, followed by fluconazole.

### Ocular Candidiasis

Ocular candidiasis can be either endophthalmitis or chorioretinitis. Disease can occur as a result of fungemia and seeding of the eye, or post-cataract surgery. Early disease (especially with chorioretinitis) may be relatively asymptomatic. Know that any patient who develops candidal fungemia should have a thorough dilated eye exam by an ophthalmologist. Postoperative patients with eye pain should have cultures of the vitreous fluid that includes evaluation for fungus.

Treatment of chorioretinitis is fairly simple with systemic antifungals, but endophthalmitis sometimes necessitates antifungals plus intravitreal amphotericin B +/- vitrectomy. **Fluconazole** is usually the initial treatment of choice because it penetrates the eye well. Amphotericin B + flucytosine is used for resistant species of *Candida*.

### Genitourinary Candidiasis

*Candida* in the urine is fairly common, especially in the hospital, and it often represents simple colonization—especially if the patient has had a urinary catheter.

Be concerned about repeatedly positive urine cultures for *Candida* in diabetics, in patients with recent urinary manipulation, and in patients with systemic signs of infection. U/A showing pyuria is not very sensitive or specific for true infection. Evaluation should include renal imaging with either U/S or CT of both the bladder and the kidneys.

Asymptomatic candiduria with negative imaging studies can be managed with only catheter change. If the patient is undergoing genitourinary procedures, IDSA recommends a course of an intravenous antifungal (ampho B deoxycholate or fluconazole) for a few days pre-procedure.

Symptomatic candiduria should be treated with a systemic antifungal (fluconazole or ampho B) based on culture results.

Know that **lipid** amphotericins do **not** penetrate the kidneys into the bladder and should **not** be used. Echinocandins are also not recommended. Bladder irrigation is also not recommended for cystitis, although it has some use in treating upper tract disease complicated by fungus balls.

Any fungus ball should be surgically removed if it is not improved after ampho B upper tract irrigation.

## CRYPTOCOCCUS

In immunocompetent patients, *Cryptococcus* usually causes minimally symptomatic, self-limited infections. Patients may have a low-grade fever, cough, and a pulmonary infiltrate—all of which resolve. It is not associated with any particular geographical location. Although it is found in old pigeon droppings, most patients have no recollection of being in contact with birds. Cryptococcal pneumonia may form cavitory lesions and peripheral “cannon ball” skin lesions.

Dissemination is more likely in T-cell-deficient patients (AIDS, corticosteroid therapy, Hodgkin disease, ALL, diabetes, and those who are post-organ transplant). These patients are especially likely to get **cryptococcal meningitis**—the most common presentation of **severe** *Cryptococcus* infection.

Suspect crypto meningitis in any immunosuppressed patient who has headache +/- skin and/or pulmonary lesions +/- fever. Lumbar puncture findings include increased CSF opening pressure, usually > 200 mm H<sub>2</sub>O. Patients with very high opening pressures are at risk for **blindness** if the pressure is not handled properly.

Confirm presence of the organism with a serum or CSF cryptococcal antigen test.

Initially treat cryptococcal meningitis with amphotericin B and flucytosine. Once the patient is clinically improved, these 2 agents can be stopped and the patient can be switched to fluconazole. Additionally, daily repeated lumbar punctures are recommended in those with increased intracranial pressure (> 200 mm H<sub>2</sub>O) or with associated headache, clouded sensorium, visual/hearing loss, or cranial nerve palsies. Sometimes shunts are required.

Patients with continued immunodeficiency (HIV/AIDS) require secondary prophylaxis with chronic fluconazole.

## ASPERGILLOSIS

*Aspergillus* species, of which *A. fumigatus* is the most commonly isolated as a pathogen, can cause severe infections, mostly in immunocompromised hosts.

Aspergillosis can present with a spectrum of disorders ranging from:

- allergic bronchopulmonary aspergillosis (an asthma-like syndrome) to
- invasive aspergillosis, which presents similar to bacterial pneumonia.

Invasive aspergillosis can be rapidly fatal and requires rapid diagnosis and treatment. The diagnosis can be made with fungal cultures. (Bronchoalveolar lavage is often required.) Alternatively, *Aspergillus* galactomanan antigen can be measured in the blood or the BAL fluid. This test is most useful in immunocompromised hosts.

First-line treatment for aspergillosis is voriconazole.

*Aspergillus* can also be the cause of fungus balls in preformed cavities in the lungs. Surgical treatment is sometimes required.

## ENDEMIC FUNGI

### Overview

These 3 organisms live in specific areas of the U.S. or are found in specific conditions. Usually a patient will become infected only after visiting or living in the area where the organism is endemic and participating in activities that encounter the organism. The 3 endemic fungi are *Coccidioides*, *Histoplasma*, and *Blastomyces*. These infections are also discussed in the Pulmonary Medicine section, Book 2.

### Coccidioidomycosis

*Coccidioides* and *Histoplasma* are dimorphs. Neither usually causes much of a problem **except** in immunocompromised patients.

The mold spores of *Coccidioides immitis* are found in the soil of the arid Southwest U.S. and northern Mexico. (This disease is often called “Valley Fever”—think of San Joaquin Valley or Death Valley.) Once inhaled, cocci converts to a yeast that, days to **weeks** later, causes a self-limited, flu-like illness with arthralgias, erythema multiforme, and/or erythema nodosum. It often has a **sarcoid-like** presentation. Disease often results in a pulmonary “coin lesion.” In immunocompromised patients, the disease is usually more severe. Think of this in a patient from Arizona with a sarcoid-like presentation.

About 22% of infected patients develop **extrapulmonary coccidioidomycosis** with disseminated bony, cutaneous, or CNS disease. Relapse is highest with CNS disease.

Most patients have self-limited disease and do not require treatment. Non-meningeal, less severe infections



## Quick Quiz

- Why are lipid amphotericin preparations not recommended in patients with funguria?
- Cryptococcal meningitis is associated with what LP abnormality?
- Empiric treatment for crypto meningitis includes what drugs?
- Where is *Coccidioides immitis* found?
- What are the clinical presentations of histoplasmosis?
- What tests are best for diagnosing various presentations of histo?
- Think about blasto in which patient populations?
- Tinea capitis requires treatment with what drug?
- Which patient groups are at risk for zygomycosis?

can be treated with either itraconazole or fluconazole. Treat severe cases with amphotericin B.

### Histoplasmosis

*Histoplasma* is confined to the Mississippi and Ohio River valleys and is especially prevalent in bat and bird droppings. Do not confuse this with the “(Death) Valley Fever” above.

Presentation of histo depends on immune status of the host. Immunocompetent patients typically have a self-limited, flu-like illness or mild pulmonary infiltrates. Histoplasmosis can present with interstitial pneumonia, palate ulcers, and splenomegaly. 1/3 have anemia, neutropenia, or pancytopenia. *Histoplasma* occasionally causes cavitary pneumonia similar to that seen in TB.

In immunocompromised patients (especially HIV/AIDS), histo can disseminate in the blood and bone marrow, causing a rapidly progressive sepsis picture and/or multisystem involvement.

Diagnosis also depends on host immune status. Immunocompetent patients can be diagnosed by pathologic evaluation of infected tissues. Serum can be sent for complement fixation antibody or immunodiffusion studies in this population. Immunosuppressed patients with disseminated disease often have positive routine and/or fungal blood cultures, as well as a positive serum and urine antigen test. The serum/urine antigen test is not very useful in patients with localized disease.

Acute pulmonary disease generally requires no therapy. More severe but localized disease can be treated with itraconazole. Treat disseminated disease with amphotericin B (either deoxycholate or liposomal formulations), followed by itraconazole.

### Blastomycosis

*Blastomyces* causes blastomycosis, a flu-like illness similar to that caused by histo and cocci above. It may also cause an acute illness that looks like bacterial pneumonia. Look for it in Arkansas and Wisconsin hunters and loggers.

Blasto disseminates to the skin, usually causing verrucous (warty) lesions with central ulceration. Bone lesions are common and may cause bone and joint pain.

Treat with itraconazole for mild-to-moderate disease and amphotericin B for CNS or severe disease.

### DERMATOPHYTES

Dermatophytes are the skin and hair fungi. These organisms are found in the soil, and they infect keratinized material; e.g., human nails and hair.

The names of the diseases caused by dermatophytes begin with “tinea” (e.g., tinea capitis, tinea corporis, tinea pedis, and tinea cruris).

Treat ringworm (tinea corporis) with topical clotrimazole or undecylenic acid. Then, if no success, itraconazole or terbinafine are the preferred oral agents. Infection of hair follicles (tinea capitis) requires treatment with an oral agent, usually griseofulvin.

### SPOROTRICHOSIS

Sporotrichosis is caused by *Sporothrix schenckii*—a dimorphic fungus associated with plants. Gardeners tend to get it, often after being pricked by a thorn. Of the 4 clinical presentations, the cutaneous and the lymphangitic (nodules form on the skin over lymph channels) types are treated with itraconazole, while the severe pulmonary and disseminated types are treated initially with lipid amphotericin B. Sporotrichosis can be a chronic problem. The disseminated type is more common in immunodeficient gardeners. *Mycobacterium marinum* and *Nocardia brasiliensis* cause similar lesions over lymphatic channels.

### ZYGOMYCOSIS

Zygomycetes cause zygomycosis (previously mucormycosis). The name of this disease has changed because more species than just *Mucor* can cause the clinical presentation (especially *Rhizopus*). Zygomycosis can be caused by *Mucor*, *Rhizopus*, or *Cunninghamella* organisms.

*Rhizopus* has special physiology that allows it to live in acidic and high-glucose conditions. It has also adapted to grow well in patients with iron overload on deferoxamine chelation. So, *Rhizopus* is especially adapted to thrive in the diabetic and in those with primary or secondary hemochromatosis. The severely immunosuppressed are also at risk.

Table 2-2: Classification of Parasites

| Group                                                                             | Subgroup                                           | Organism                                                                                                                      |
|-----------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>PROTOZOA</b><br>(Do replicate within the body)<br>(no eosinophilia)            | Sporozoa                                           | <i>Toxoplasma</i> , <i>Cryptosporidium</i> , <i>Isospora belli</i> , <i>Plasmodium</i> , <i>Pneumocystis</i> , <i>Babesia</i> |
|                                                                                   | Ameba                                              | <i>Entamoeba histolytica</i>                                                                                                  |
|                                                                                   | Flagellates                                        | <i>Giardia</i> - GI; <i>Trichomonas</i> - GU<br><i>Leishmania</i> , <i>Trypanosomes</i> - blood                               |
| <b>HELMINTHS</b><br>(Do <b>not</b> replicate within the body)<br>(+ eosinophilia) | Nemathelminthes<br>(= nematodes)<br>(= roundworms) | Pinworms, Hookworms, Whipworms ( <i>Trichuris trichiura</i> ), <i>Trichinella</i> , <i>Strongyloides</i>                      |
|                                                                                   | Platyhelminthes                                    | Cestodes (tapeworms); Trematodes (flukes)                                                                                     |

Disease can present as invasive pulmonary or rhinocerebral infection. Rhinocerebral mucormycosis starts as a **black necrotic** spot in the **nose** or paranasal sinuses, and extends **intracranially**; it has a **poor** prognosis.

Know that these zygomycetes, like *Aspergillus*, cause a **necrotizing, cavitating pneumonia**. Rule out zygomycosis in a patient on voriconazole treatment or prophylaxis with new or worsening pulmonary disease.

Treat with aggressive surgical management and lipid amphotericin B. Posaconazole can be used as an option in those who cannot tolerate amphotericin B or for salvage therapy.

## PARASITES

### PROTOZOA

#### Overview

There are 2 main types of parasites: **protozoa** and **helminthic organisms**. See Table 2-2.

The protozoa are **single-celled** and can replicate within the body, so it takes only a small number of organisms to cause infection. Protozoa do **not cause eosinophilia**.

The 3 types of protozoa are:

- 1) Sporozoa (*Toxoplasma*, *Cryptosporidia*, *Isospora*, *Plasmodium*, *Babesia*)
- 2) Ameba (*Entamoeba histolytica*)
- 3) Flagellates (*Giardia*, *Trichomonas*, *Trypanosoma*, *Leishmania*)

#### Sporozoa

##### *Toxoplasma gondii*

*Toxoplasma gondii* is the protozoan that causes toxoplasmosis. Cats are the definitive host since **all** the oocysts (infectious forms) that eventually infect humans are shed in cat feces. It is common; 2/3 of adults have had it.

There are 4 types of toxoplasmosis:

- 1) Toxoplasmosis in the immunocompetent is most often **asymptomatic**, but may cause nontender lymphadenopathy, night sweats, and atypical lymphs. Self-limited. Diagnosis can be made by observing a rise in acute and convalescent serum IgG and IgM titers.
- 2) **Congenital** toxoplasmosis. The only time *Toxoplasma* is of real concern in immunocompetent people is if it is acquired during **pregnancy**, when it can infect the fetus and cause congenital toxoplasmosis—causing mental retardation and necrotizing chorioretinitis. The fetus is more likely to have a congenital infection if the disease is acquired later in pregnancy (15%: 1<sup>st</sup> trimester; 70%: last trimester), but those infected later in pregnancy are usually **asymptomatic**. Diagnosis can be made by observing a rise in acute and convalescent serum IgG and IgM titers.
- 3) **CNS** toxoplasmosis occurs in immunocompromised patients with reactivation of previous infection. These patients present with **multiple CNS mass lesions**. Because this is reactivation disease, serum titers do **not help** in diagnosis. Most of these patients already have anti-*Toxoplasma* IgG. A negative IgG also does not necessarily exclude infection because sometimes AIDS patients have difficulty making antibodies. AIDS patients remain on therapy for life unless immune reconstitution (normalized CD4 counts) has occurred with antiretroviral therapy. Treat with pyrimethamine + sulfadiazine and leucovorin.
- 4) **Ocular** toxoplasmosis causes retinal lesions that look like yellow-white cotton patches, and also irregular scarring and pigmentation (disseminated candidiasis produces white cotton wool patches). Treatment consists of pyrimethamine and a sulfonamide (sulfadiazine or trisulfapyrimidine) for 3 weeks.

##### *Cryptosporidium*

*Cryptosporidium* is a protozoan that causes infection, especially in the immunocompromised but **also** in the immunocompetent. The oocytes are passed in animal (including human) feces (vs. just cats in toxo). Symptoms in immunocompetent patients usually



## Quick Quiz

- How is serology useful in making a diagnosis of CNS toxoplasmosis?
- In a patient with diarrhea and a history of ingesting fresh raspberries, what organism do you think of?
- Which form of malaria is associated with the banana-shaped gametocyte?
- Chloroquine is useful against which species of malaria?

consist of a watery diarrhea, which is self-limited, lasting 1–2 weeks. In the immunosuppressed, it can persist indefinitely and is **refractory** to medications. Diagnose by **acid-fast** stains (small and round). Immunocompetent patients may be treated with nitazoxanide.

### *Isospora belli*

*Isospora belli* is another acid-fast protozoan that causes a watery diarrhea in patients with AIDS, similar to *Cryptosporidium*. On the acid-fast stain, it is large and oval, whereas *Cryptosporidium* is small and round. Treat with TMP/SMX.

### *Cyclospora*

*Cyclospora* is an acid-fast intestinal protozoan parasite that causes diarrhea in both immunocompromised and immunocompetent patients. Clue: **raspberries** from Central America! Systemic symptoms such as malaise, myalgia, low-grade fever, and fatigue are commonly seen with *Cyclospora* infection. Treat with TMP/SMX.

## Malaria

### Overview

There are 5 disease-causing *Plasmodium*:

- 1) *P. falciparum*
- 2) *P. vivax*
- 3) *P. ovale*
- 4) *P. malariae*
- 5) *P. knowlesi*

*Plasmodium* is a protozoan that causes malaria. It infects the RBCs and is transmitted via the *Anopheles* mosquito. Asplenic patients have more severe infections. **Any** type of malaria can cause **nephritis** from immune complex deposition, but *P. malariae* is most commonly associated with **nephrotic** syndrome.

As we go through the following, see [Table 2-3: Treatment and Prophylaxis of Malaria](#).

### *P. falciparum*

*P. falciparum* causes the most severe malaria; it is the cause of virtually all fatal infections. It also has **widespread chloroquine resistance**. Most cases of *P. falciparum* are acquired in mid-Africa.

The blood smear in *P. falciparum* shows **diagnostic** “banana-shaped gametocytes,” and often you see more than 1 infected RBC on the slide, and even multiple parasitized RBCs ([Image 2-15](#)).

This contrasts with the other forms of malaria in which the parasitized RBCs are often hard to find. Even though *P. falciparum* causes the highest levels of parasitemia, the schizonts are **not** seen on peripheral smear. If you see schizonts, the patient has one of the other types.

Treatment of *P. falciparum* malaria:

- Chloroquine-sensitive: Give chloroquine (of course).
- Chloroquine-resistant, moderately ill: Give
  - atovaquone/proguanil,
  - mefloquine, or
  - artemisinin derivatives (artesunate, artemether).
- Severe *P. falciparum*: Give artemisinin derivatives, such as artesunate, because these drugs clear the blood of parasites faster than quinine drugs.

### Non-*falciparum*

The **Duffy** RBC antigen is the site of attachment for *P. vivax*.

Treatment of non-*falciparum* malaria:

Use **chloroquine** for **non-*falciparum*** infections. **Primaquine** is adjunctive medication for infections with *P. vivax* and *P. ovale* to eradicate hypnozoites in the liver. Hypnozoites are the malarial forms responsible for relapse. Some *P. vivax* isolates are resistant to chloroquine and can be treated with mefloquine, atovaquone-proguanil, or quinine + doxycycline.

Remember that primaquine induces **hemolytic anemia** in G6PD-deficient persons, so you **must screen** for G6PD deficiency before prescribing it.

Prophylaxis:

For malaria **prophylaxis**, use chloroquine if **no** chloroquine-resistant *P. falciparum* malaria is present in the area in question. Start it 1–2 weeks before patient departs to the endemic area and continue 4–6 weeks after she leaves the area.

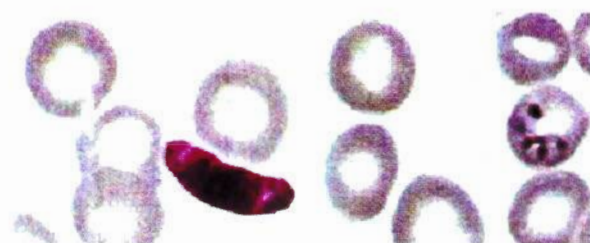


Image 2-15: *P. falciparum*, “banana-shaped gametocytes”

Table 2-3: Treatment and Prophylaxis of Malaria

| Type of Malaria                                                 | Treatment                                                                                         | Prophylaxis                                                                                                                                                            |
|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non- <i>falciparum</i> malaria                                  | Chloroquine and primaquine                                                                        | Chloroquine 500 mg (300 mg base) weekly. Give daily in endemic areas.                                                                                                  |
| <i>P. falciparum</i><br>Chloroquine-sensitive                   | Chloroquine<br>Atovaquone/proguanil                                                               | Choose any one of the following:<br>Chloroquine<br>Atovaquone/proguanil<br>Mefloquine<br>Doxycycline                                                                   |
| <i>P. falciparum</i><br>Chloroquine-resistant<br>Moderately ill | Atovaquone/proguanil<br>or<br>Mefloquine<br>or<br>Artemisinin derivative (artesunate, artemether) | Mefloquine: one dose weekly, including 1 week before and 4 weeks after<br>or<br>Atovaquone/proguanil: one dose daily, including 1–2 days before and 7 days after<br>or |
| <i>P. falciparum</i><br>Chloroquine-resistant<br>Very ill       | Artemisinin derivative (best choice) or<br>IV quinidine gluconate +/- IV clindamycin.             | Doxycycline: 100 mg 1–2 days before travel and continued 4 weeks after return                                                                                          |

Use mefloquine or atovaquone/proguanil for prophylaxis in chloroquine-resistant areas. Primaquine can be given the **last 2 weeks** of a prophylaxis period after travel to areas where there is *P. vivax* or *P. ovale*. Know that the **main causes** of malaria in the U.S. are either not taking prophylaxis or stopping prophylaxis too soon after returning from travel to endemic areas!

Atovaquone/proguanil is considered the drug of choice for prophylaxis. Specifically, the main advantage is that it can be started just prior to leaving and stopped soon after return—and has fewer side effects. The disadvantage is that it must be taken daily.

Doxycycline has activity against chloroquine-sensitive and chloroquine-resistant malaria, and it can be used for prophylaxis at a dose of 100 mg daily. The advantage is that it is very inexpensive. The disadvantages are that it can cause photosensitivity, has to be taken daily, and has to be taken for 4 weeks after leaving the endemic area.

### Babesia

*Babesia microti* is an intra-RBC protozoan parasite that causes babesiosis. This disease is a **febrile, hemolytic anemia** seen especially in debilitated elderly patients and **asplenic** patients. The organism is transmitted via the *Ixodes* tick from rodents, as is the spirochete *Borrelia*, which causes Lyme disease. It is most prevalent in the Northeast U.S.—usually in summer or early autumn. Asplenic patients have more severe disease.



Image 2-16: Maltese Cross—*Babesia microti*

Symptoms, which may persist for **months**, include fever, profuse sweats, myalgias, and shaking chills. **Hemoglobinuria** is a predominant sign. Patients often are emotionally labile. Because of the symptoms and the parasitized RBCs, it may be misdiagnosed as malaria.

*B. microti* is distinguished from *Plasmodium* by the classic intra-RBC pear shapes, which occasionally form a tetrad appearing as a “Maltese Cross.” (See Image 2-16; the malarial parasites have a **ring** form.)

Mild babesiosis infections are usually self-limited. Treat moderate infections with atovaquone + azithromycin. If severe, treat with clindamycin + quinine and consider an exchange transfusion.

Again: Asplenic patients have more severe disease.

### Ameba

Human amebiasis is caused by the protozoan *Entamoeba histolytica*. Transmission is fecal-oral and can be food- or waterborne. In the U.S., the usual population groups in which it is found are the institutionalized, immigrants, and men who have sex with men. For intestinal disease, diagnose by examining the stool. However, the aspirate of an amebic liver abscess often shows **no** ameba or PMNs—confirm the diagnosis of this extraintestinal manifestation with **serology**.

Treat with metronidazole—even large amebic abscesses respond very quickly. After you treat the abscess, give treatment for intraluminal disease, even if the stool sample did not show organisms. Use paromomycin or iodoquinol.



## Quick Quiz

- For travel to chloroquine-resistant areas, what drugs are used for malaria prophylaxis?
- What is the presentation of *Babesia* infection?
- How do you diagnose and treat extraintestinal amebiasis?
- How is a *Giardia* infection diagnosed?
- What is kala-azar?

### Flagellates

The flagellates: *Giardia lamblia*, *Trichomonas vaginalis*, *Trypanosoma*, *Leishmania*.

#### *Giardia lamblia*

*Giardia* infections are found in campers, travelers, children in day care, HIV+, men who have sex with men, and in patients with IgA deficiency and/or hypogammaglobulinemia. It infects the duodenum. 75% of infected persons are asymptomatic. Acute symptoms include a watery, smelly diarrhea and flatulence. Chronic giardiasis causes flatulence, sulfuric belching, and soft stools. Diagnose with microscopic examination of **fresh stool samples x 3** or ***Giardia* antigen test** on 1 stool. For chronic giardiasis, consider a string test: Have the patient swallow a capsule on a string, leave it for several hours, then retrieve it and check for trophozoites. Note that this is rarely done today.

Treat giardiasis with:

- metronidazole (not an FDA-approved use), or
- tinidazole (FDA-approved).

Several **other** agents can be used, including:

- Albendazole (in children)
- Furazolidone (doesn't work as well as metronidazole)
- Nitazoxanide (possibly superior to metronidazole)
- Bacitracin
- Paromomycin in pregnancy

#### *Trichomonas vaginalis*

*Trichomonas vaginalis* causes an STD. Treat with metronidazole. More under Vaginitis, [page 2-62](#).

#### *Trypanosomiasis*

*Trypanosoma* causes trypanosomiasis. There are 2 main types. The African disease is **sleeping sickness**, which is caused by *Trypanosoma brucei* and transmitted via the tsetse fly. The American illness, **Chagas disease**, is caused by *T. cruzi* and is found in South America and Mexico. Usually, it is self-limited, but the chronic form can cause problems with the heart (from heart block to CHF), the GI system (especially achalasia,

megaesophagus, and megacolon, as discussed in the Gastroenterology section, Book 1), and occasionally the CNS. Treat with antimonials and arsenicals obtained from the CDC. Note: Chagas disease is the most common cause of CHF in Brazil.

#### Leishmaniasis

Leishmaniasis is caused by any of the following 4 species of the *Leishmania* protozoa: *L. donovani*, *L. tropica*, *L. mexicana*, and *L. braziliensis*. *L. donovani* is spread by sand flies and causes visceral leishmaniasis, also called **kala-azar**. These patients get GI symptoms, hepatomegaly, and sometimes huge splenomegaly. The other species cause cutaneous and mucocutaneous forms of the disease. Recent reports indicate there is a higher susceptibility for leishmaniasis in HIV-infected patients who travel to endemic areas.

Sodium stibogluconate (pentavalent antimony), pentamidine, or amphotericin B are the treatments of choice.

## HELMINTHIC ORGANISMS

### Overview

The helminthic organisms are the other major type of parasite. (Remember: 1) protozoa and 2) helminthic organisms.) Helminthic organisms are **multicellular worms** that, in general, do **not replicate** in the body—and they **do** cause eosinophilia. Helminthic organisms consist of nematodes, tapeworms, and flukes.

Know that for each of the helminthic infections associated with poor sanitation, effective sanitation is the long-term solution. Reinfection in endemic areas is common unless the people use strict preventive measures (e.g., cleaning of ingested food and water, good personal hygiene, wearing shoes, etc.).

Remember: With the exception of *Strongyloides*, helminthic organisms do **not** multiply in the human body.

### Nematodes

Note that nematodes, as a whole, are called roundworms, but the common term for *Ascaris* is also roundworm.

We will discuss 10 types of nematodes:

- 1) *Ascaris lumbricoides* (roundworm; causes ascariasis) ([Image 2-17](#)). Worldwide, > 1 billion people infected and the sole host is humans. In U.S., 2% overall infected. Worse in rural South with up to 30% of young children affected in some areas. Associated with poor sanitation. Life cycle: Eggs are ingested, hatch in the small intestine, and the larvae penetrate the intestinal wall and migrate to the lungs where they mature over 10 days. Then they ascend the bronchial tree and are swallowed. They then mature into adult worms in the small intestine. Eggs are excreted in the stool. Eggs can live for up to 10 years in dark moist conditions. Main treatment is albendazole or mebendazole.

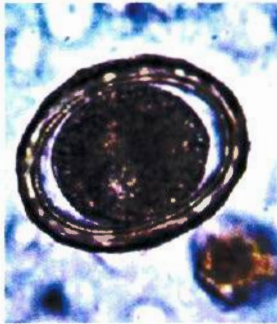


Image 2-17: Roundworm egg



Image 2-18: Pinworm eggs

- 2) *Enterobius vermicularis* (pinworm; causes rectal itching) (Image 2-18). Most common helminthic infection in U.S. Humans are the only host. Life cycle: Eggs are ingested and hatch in the small intestine. Gravid females migrate to the rectum and, at night, lay eggs in the perianal area. Even though most infections are asymptomatic, the worms and eggs in the perianal area occasionally cause the most common symptom of pruritus ani (perianal itching). Diagnose with the “scotch tape” test where tape which has been placed on the perianal skin is viewed under the microscope. Main treatment is a single dose of albendazole or mebendazole; repeat in 2 weeks. Good sanitation and personal hygiene.
- 3) *Necator americanus* (hookworm). Requires coming into contact with human feces in the soil. Associated with poor sanitation. Especially at risk are people walking barefoot or with open sandals in contaminated areas. Nutritional deficiency and anemia are the main problems. Occasionally causes serpiginous skin lesions similar to cutaneous larva migrans. Life cycle: Larvae penetrate the skin and migrate to the lungs. They then migrate up the bronchial tree and are swallowed. Once in the small intestine, they mature and attach to the intestinal wall, getting nourishment from extravasated blood. Eggs are excreted in the stool. Main treatment is albendazole or mebendazole.
- 4) *Trichiura* (whipworm) affects over 1.5 billion people worldwide. Found in warm moist places with poor sanitation, similar to *Ascaris*. People often have coinfection with *Ascaris*. Life cycle: Eggs ingested, hatch in small intestine, mature in caecum and ascending colon; eggs excreted in stool. Main treatment is albendazole or mebendazole.
- 5) *Trichinella* consists of 8 species and many genotypes. Seven species cause disease in humans, *T. spiralis* the main one in the U.S. The main sources of the disease are from undercooked wild game (e.g., bear, wild boar) and domesticated pigs. Causes trichinosis (trichinellosis). In the U.S., only 66 cases were reported between 2002 and 2007, although there is a much higher incidence on autopsy. Life cycle: Eggs are ingested and larvae attach to the small intestine wall. Larvae are released and these larvae spread via the blood vessels to

the muscle, where they burrow and encyst in a muscle cell. Symptoms are due to the phase when larvae burrow into muscle cells causing muscle pain, tenderness, and weakness. Serious infections can affect the CNS, lungs, heart, and kidneys. Treatment for mild cases is supportive. For serious infections, treat with albendazole or mebendazole and glucocorticoids.

- 6) *Wuchereria bancrofti* is transmitted by the mosquito. More than 100 million people worldwide are infected, and 1/3 of those are symptomatic. It is the main cause of **lymphatic filariasis**. This filariasis causes lymphatic inflammation. In more severe cases, lymphatic blockage occurs. Very severe cases cause elephantiasis. Symptoms include:
  - Acute fever—called **filarial fever**. Easily confused with malaria.
  - Acute fever and painful and tender lymphadenopathy—called **acute adenolymphangitis**.
  - Nighttime wheezing—called **tropical pulmonary eosinophilia**. Caused by microfilariae in the lungs. Life cycle: Mosquito introduces larvae into skin during feeding. Larvae enter the lymphatics and mature over 9 months. Adult worms then produce microfilariae that migrate into the bloodstream where they are picked up by feeding mosquitos. Diagnose by finding microfilariae in the blood. Patients typically have high eosinophilia. Main treatment is diethylcarbamazine (DEC).
- 7) *Strongyloides stercoralis* is endemic in tropical regions of the world and, in the U.S., is seen in people from endemic areas and in those living in the southeastern states. It is (virtually) **the only helminthic organism that replicates in the body**. With this autoinfection, the infection can persist for decades (*Strong!*). Symptoms are usually GI, but there can be pulmonary symptoms during the infective part of the larvae's life cycle. Eosinophilia usually is present. In immunosuppressed patients, potentially fatal **disseminated** strongyloidiasis may occur—presenting with abdominal pain and distention, neurologic and pulmonary symptoms, and shock. Like *Necator* (hookworm), the larvae of *Strongyloides* are found in soil contaminated with human feces. Life cycle: Also like hookworm, the *Strongyloides* larvae penetrate the skin and migrate to the lungs. They then migrate up the tracheobronchial tree and are swallowed. Once in the small intestine, they attach to the mucosa and mature. Adult female worms produce **non-infectious** larvae that are mostly excreted in the stool. Some of these noninfectious larvae convert to infectious filariform larvae while still within the small intestine. These larvae penetrate the wall of the colon or perianal skin to reinoculate. *S. stercoralis* is the **only** helminth that is able to **autoinfect**. That is, complete the **entire life cycle** and **replicate** within **one** host. Diagnose with serial stool samples. Treat with ivermectin or albendazole.



## Quick Quiz

- Disseminated strongyloidiasis can be seen in which patient population?
  - What is visceral larva migrans?
  - When do you not treat patients with neurocysticercosis with an antiparasitic drug?
- 8) *Toxocara canis* causes toxocariasis, also called **visceral larva migrans** (LVM). *Toxocara cati* from cats less commonly cause the same syndrome. It occurs worldwide with a 14% prevalence in the U.S. Humans are **not** normal hosts for these helminths and are **not** a required part of their life cycle. LVM presents with fleeting, migratory pulmonary infiltrates that self-resolve. These also cause ocular larva migrans (OLM) with ocular symptoms. The normal hosts for *Toxocara canis* are dogs, and it is transmitted to humans by ingesting soil contaminated with dog excrement. In humans, the larvae do not develop into adult worms but rather migrate through the host tissue—eliciting eosinophilia. Treat with albendazole or mebendazole.
- 9) *Angiostrongylus cantonensis* is the rat lungworm. It causes eosinophilic meningitis in patients who ingest the larvae along with their intermediate hosts: snails, vegetables contaminated by snail slime, crabs, and freshwater shrimp. Typically, disease in the U.S. occurs in travelers returning from the South Pacific.
- 10) *Baylisascaris procyonis* is a roundworm that causes eosinophilic meningitis. It is transmitted, usually to children, via ingestion of infected raccoon droppings. The disease is very rare.

## Tapeworms

The **pork tapeworm**, *Taenia solium*, causes 2 clinical presentations:

- 1) If the cysticerci are ingested, **taeniasis** develops. (A tapeworm grows in the intestines.)
- 2) If an egg-contaminated (from animal or human feces) food is ingested, the patient will develop **cysticercosis**. In this, the eggs hatch and the oncospheres go into the blood and, most significantly, cause cysticerci in the CNS and eyes. These cysts do nothing **until the organism dies**. In the brain (**neurocysticercosis**), the resulting inflammation usually causes seizures as the 1<sup>st</sup> symptom. Especially consider cysticercosis in a patient with new-onset seizures who is a Mexican immigrant or is from a household with a Mexican immigrant.

Niclosamide is the usual treatment for all **intestinal** tapeworms. Albendazole (1<sup>st</sup> choice) or praziquantel are the antiparasitic drugs used to treat neurocysticercosis. Antiepileptic treatment is important in patients with

inflamed brain lesions or with a history of seizures and calcified lesions. These patients (and those with disease of the extraocular muscles or optic nerve) should be treated with an antiparasitic plus corticosteroids. If cerebral edema or lots of inflammation is present, hold off on treating with antiparasitics and give corticosteroids only. No treatment is necessary for patients with only calcified lesions and no history of clinical disease. Cutaneous and intramuscular disease can be treated with analgesics.

The other tapeworm to be aware of is the *Echinococcus*. Most cases are diagnosed in immigrants from China, South and Central America, the former Soviet Union, and the Middle East. Initial phase of infection is usually asymptomatic and most people are infected as children. The liver is the most common organ affected followed by the lungs. The right lobe of the liver is most commonly affected and usually presents as a single large cyst. Complications can occur if the cyst ruptures into the biliary tree or peritoneum. Ultrasound or other imaging is diagnostic with a serologic test (ELISA usually). Treatment with newer surgical techniques is evolving; but open surgery is recommended for large cysts (> 10 cm), and chemotherapy with albendazole or mebendazole before and after surgery is useful.

## Flukes

*Clonorchis sinensis* is the **Chinese liver fluke**, which is endemic in the Far East. Infection is caused by eating **raw fish**, and it is often associated with **biliary obstruction**.

*Schistosoma haematobium* infects the **bladder**, causing urinary symptoms. *Schistosoma mansoni* is a fluke found in Africa, the Middle East, and South America. *Schistosoma japonicum* is found in Asia.

*Schistosoma* causes acute **schistosomiasis** (Katayama fever) ~ 2 months after inoculation. This infection presents with fever, lymphadenopathy, **diarrhea** (DDx: travelers' diarrhea), hepatosplenomegaly, and marked eosinophilia. The most serious complication of schistosomiasis is **cirrhosis** with **esophageal varices**. Schistosomiasis does **not** cause the other stigmata seen with alcoholic cirrhosis (e.g., spiders, gynecomastia, or ascites).

Diagnosis: finding the eggs in the stool or urine for *S. haematobium*.

Treatment: praziquantel—give for **1 day!**—for any *Schistosoma* and most other fluke infections.

## VIRUSES

### HERPES SIMPLEX VIRUS (HSV)

Herpes Simplex Virus (HSV): a **DNA** virus. Many HSV infections are spread by asymptomatic shedding of virus.

**HSV-1** causes orofacial infections in ~ 40% of the population. In the primary infection, the vesicular lesions and ulcers are usually localized to the



oral mucosa, lips, and surrounding skin, whereas in recurrent infections, ulcers are usually on the outer lip. It is possible to autoinoculate the virus, so the infection can spread from the lips (or other areas) to the eyes of a patient.

Recurrent HSV-1 eye infection resulting in a **keratitis** is the most common **infectious** cause of blindness in industrialized nations.

**Tzanck** smears are performed by scraping down to the bottom cellular layer of a vesicle, placing the material on a slide, then staining with either Giemsa or Wright. In herpes simplex and varicella, it will show **multinucleated giant cells** (Image 2-19). Most centers no longer perform the Tzanck smear because it is neither sensitive nor specific—nevertheless, be able to recognize the smear because it commonly appears in Board-testing situations. Viral culture, PCR, and DFA have become the gold standards depending on the clinical situation. The use of a HSV DFA (direct fluorescent antibody) test on lesions has become available in many centers.

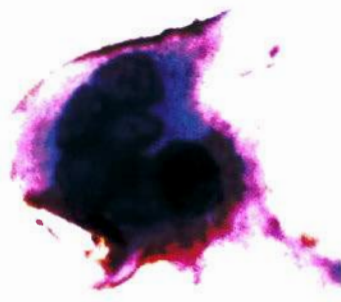


Image 2-19: Multinucleated giant cell

**HSV-2** causes “genital herpes.” Actually, it causes about 75% of HSV genital infections—the rest are due to Type 1. Note that the prevalence of HSV-2 is 25%, and of those, only 25% have symptoms! In 10% of patients, the initial occurrence of HSV-2 is associated with only a herpetic exudative pharyngitis. Most cases of neonatal HSV are from **intrapartum** contact, so a **C-section** is recommended if the mother has symptoms or signs of genital herpes, or its prodrome, at the time of delivery. The risk for transmission to the neonate is high (30–50%) among women who get their 1<sup>st</sup> episode of genital herpes near the time of delivery and is low (< 1%) among women with a history of recurrent herpes. HSV reactivates in 2/3 of seropositive **transplant** patients within 6 weeks of transplant, but this rate is drastically **lower** in patients receiving antiviral prophylaxis.

HSV causes the highest number of deaths due to encephalitis in adults. (The most commonly **identified** etiologies are due to arboviruses, but the majority of encephalitis cases today are still **not** identified.) Patients with herpes encephalitis usually present with constitutional symptoms and **altered mental status**, and may have **focal** neurologic signs. Because it has a predilection for the temporal lobe, patients may have temporal lobe seizure symptoms (abnormal behavior, smells burning rubber). More than 60% will have neurologic sequelae!

CSF usually shows increased protein, lymphocytic pleocytosis, and increased red cells, but it can be normal

in early infection. Identification of HSV DNA by PCR on CSF is the most sensitive diagnostic test. MRI may show abnormalities in the temporal lobes.

HSV is one of the many causes of erythema multiforme. (See the Dermatology section, Book 5.)

Treatment of HSV: Use IV **acyclovir** for **serious infections** and in immunosuppressed patients. Give it or one of its analogs (famciclovir, valacyclovir) orally for genital herpes. Acyclovir (or famciclovir or valacyclovir) can also be given chronically to suppress infection, or as a treatment for acute recurrence. Use **foscarnet** to treat those with HSV resistant to acyclovir; **ganciclovir is not used** because cross-resistance is common in acyclovir-resistant strains.

## VARICELLA-ZOSTER VIRUS

### Overview

Varicella-zoster virus (VZV; **DNA**) causes chicken pox (Image 2-20) and herpes zoster (shingles).

### Chicken Pox

Chicken pox is an airborne, highly contagious disease that causes a characteristic pruritic vesicular eruption that comes in successive crops. On exam, these skin lesions are typically found in various stages of healing, from new erythematous papules, to vesicles, to crusted-over lesions.

Patients are contagious for 1–2 days before eruption and stay contagious until the last lesion has crusted over. These pox marks do not leave scars unless superinfected.

Adolescent and adult patients also have a characteristic prodromal phase with fever, malaise, pharyngitis, myalgias, nausea, and headache. Children have a short prodromal phase (< 24 hours) or a papular rash may be the first symptom.

Chicken pox symptoms are usually mild in children but may be severe in adolescents and adults, and especially in **adult males** and **pregnant women**. Pneumonia is more likely to occur. In pregnancy, besides increased severity and pneumonia, birth defects are more likely if the mother is infected between 8 and 20 weeks.

Diagnosis is clinical.

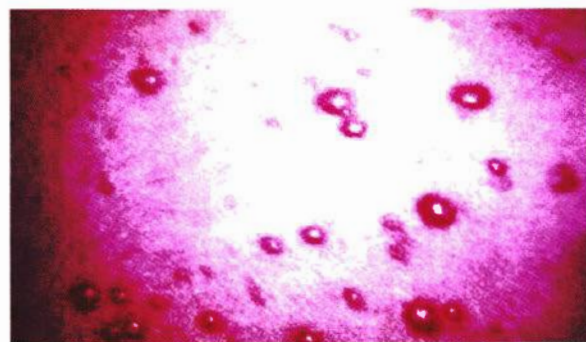


Image 2-20: VZV: Chicken pox

Courtesy, CK Dr. K. J. Hermann



## Quick Quiz

- Multinucleated giant cells can be seen associated with which infection?
- When are most cases of neonatal HSV infection acquired?
- What is the most sensitive method for diagnosing HSV encephalitis?
- In what situation should a pregnant woman be given varicella vaccine?
- Which patients should receive the zoster vaccine?

Treatment: Current recommendation is for pregnant patients exposed to chicken pox or shingles to receive zoster immune globulin (VariZIG™) within 4 days of exposure. After 4 days, it does no good. Do not **ever** give varicella virus vaccine (Varivax®) to pregnant patients because it is a **live** vaccine.

Most authorities recommend treating exposed adults/adolescents only if they present within the first 24 hours of the exanthem. These patients are given oral acyclovir 800 mg tid x 5 days. Give IV acyclovir to immunocompromised patients, but be aware that the dosing is **higher** for **VZV**, than when treating HSV.

## Herpes Zoster (Shingles)

### Overview

Herpes zoster is caused by reactivation of the varicella-zoster virus decades after the initial infection. With the initial infection, the virus does not disappear. Instead it becomes dormant and asymptomatic, living in nerve cell bodies until it is reactivated and spreads down the nerve causing a painful rash.

Reactivation causes a prodromal phase with constitutional symptoms followed by hyperesthesia and a burning, frequently lancinating pain over the dermatome. This is followed by the characteristic vesicular skin rash.

Usually one thoracic dermatome is involved, but occasionally it may involve 1–2 more. About 10–20% of patients have involvement of the ophthalmic branch of the trigeminal cranial nerve. This can be sight-threatening if zoster keratitis results.

Just as with chicken pox, the zoster patient is highly contagious until the lesions are crusted over—and can give a nonimmunized person chicken pox.

Disease duration is about 2–4 weeks. If there are any new lesions after 7–10 days, consider underlying cell-mediated immunodeficiency. Immunocompromised patients have more severe symptoms.

Shingles recurs in < 5% of immunocompetent patients.

## Postherpetic Neuralgia

Postherpetic neuralgia is the most common complication (~ 12% overall) of zoster, and it is more likely to occur with increasing age (20% in those > 80 years of age). It can cause a lancinating, sometimes debilitating pain for many months to years.

## Vaccination for Herpes Zoster

The zoster vaccine decreases the incidence of zoster by **1/2** and the incidence of postherpetic neuralgia by **2/3**! In 2006, the FDA approved and the Advisory Committee on Immunization Practices (ACIP) recommended herpes zoster vaccination for all people **≥ 60 years** of age. It is **not** recommended for pregnant women or those with immunodeficiencies (live virus vaccine). It is **not** recommended for the **treatment** of current zoster or postherpetic neuralgia. In 2011, the FDA approved the drug for those 50–59 years of age, but the ACIP declined to recommend the vaccine for this age group because of current shortages of the vaccine already for those **≥ 60**.

## Treatment

Only **famciclovir** and **valacyclovir** are shown to decrease the **incidence** of postherpetic neuralgia. High-dose oral acyclovir is an option, and, although it shortens the course of acute illness a little, it does **not** decrease the incidence of postherpetic neuralgia.

Valacyclovir is an L-valyl ester of acyclovir, has 3–5x greater bioavailability than acyclovir, and is almost completely converted to acyclovir after oral administration.

Adding prednisone provides **no** additional benefit and even **prolongs** the course of herpes zoster in **immunosuppressed patients**.

For pain control, tricyclics, gabapentin, and lidocaine patches have some efficacy. Narcotics are effective and underused in this instance. Capsaicin cream is useful after the lesions have healed.

If a patient presents with back pain and you think it is a herpes zoster prodrome, what should you do? Answer: Nothing, except follow closely. The acyclovir, or one of its analogs, is not started until you see the vesicles.

## CYTOMEGALOVIRUS (CMV)

Cytomegalovirus (CMV) is a **DNA** virus. CMV infection in the normal population is fairly common; 1/2 of the population has anti-CMV antibodies by the age of 35.

CMV infection in the **normal** population is usually asymptomatic, but ~ 10% have a **mononucleosis-type illness** with fever, sore throat, adenopathy, fatigue, and hepatitis. Think of this in a monospot-negative adult with these symptoms (especially if **younger-to-middle-aged** because EBV mono usually occurs more in adolescents). Also, consider **acute HIV** with this presentation.

CMV is a very common infection in patients with decreased **cellular** immunity (post-transplant and AIDS). 75% of seronegative transplant recipients get CMV if the **donor** is seropositive. With a post-transplant systemic CMV infection, the patient can have concurrent “-itises,” which may include encephalitis, hepatitis, retinitis, colitis, and adrenalitis (causing adrenal insufficiency); these are especially common and more severe if the recipient is **seronegative** prior to the transplant.

**HIV/AIDS:** When the CD4 count gets < 100, CMV can cause **chorioretinitis**, **pneumonitis**, **esophagitis**, and **colitis**. This CMV retinitis is distinctive; it has both retinal blanching and hemorrhage.

The diagnosis of acute CMV infection is usually straightforward, and can be accomplished by demonstrating DNA or antigen in peripheral blood. For tissue invasive disease, virocytes, which stain with specific immunohistochemistry, can be seen. Occasionally, tissue-invasive disease presents without viremia.

Previously, CMV retinitis treatment involved lifetime IV ganciclovir or foscarnet. Now with oral valganciclovir (a ganciclovir prodrug) and ganciclovir intraocular implants, treatment is much easier and more tolerable. Treatment now consists of either oral valganciclovir alone (as good as IV ganciclovir) or oral valganciclovir plus a ganciclovir intraocular implant (better than IV ganciclovir).

## EBV

Epstein-Barr Virus (EBV; **DNA**) causes infectious mononucleosis. Incubation period is 1–2 months. Most (> 90%) patients have pharyngitis or tonsillitis, fever, lymphadenopathy, and abnormal liver function.

EBV causes **hairy leukoplakia**; this mucocutaneous lesion may be seen as an early manifestation of HIV disease. Chronic fatigue has **no** proven association with EBV. EBV is associated with nasopharyngeal carcinoma and Burkitt lymphoma.

Lymphocytosis is commonly found in EBV-infected patients with > 10% atypical lymphocytes: enlarged with abundant cytoplasm, vacuoles, and indentations



Image 2-21: Rubella infection with postauricular adenopathy

of the cell membrane. 50% have splenomegaly. Most develop a macular rash if given ampicillin.

Heterophile antibody titers (**monospot**) decrease within 6 months, but the EB IgG antibodies are present for years. The atypical lymphs are **T cells**. A patient with mononucleosis symptoms who is heterophile-negative usually has CMV. Recurrence of mono is unusual but possible—usually with high titers of antibody to EB antigen (> 1:5,000).

## RUBELLA (GERMAN MEASLES)

Rubella is “German measles” (ssRNA virus; **Image 2-21**). If it is acquired by a pregnant patient in the **1<sup>st</sup>** trimester, there is a 50% chance that the baby will have congenital defects. It is diagnosed by the hemagglutination inhibition test. If this test is negative in a newly exposed pregnant patient, repeat it in 3 weeks (after incubation period) before any decisions are made. If it is then positive, offer the patient the option of a therapeutic abortion. Immune globulin does not prevent the infection, but it **may** give some fetal protection in the patient who refuses therapeutic abortion.

## RUBEOLA (MEASLES)

Rubeola is “measles” caused by an ssRNA virus. Symptoms start ~ 10 days after the initial exposure. Symptoms at the onset: the “3 Cs”: cough, coryza, and conjunctivitis (with photophobia). Patients also have malaise and fever. **Koplik spots** (whitish spots on an erythematous base) appear on the buccal mucosa before the onset of the skin rash (**Image 2-22**). The skin rash starts at the hairline and spreads downward. It lasts ~ 5 days and then resolves, also from the hairline downward. Again: 3 Cs, Koplik spots, rash. Outbreaks continue to occur, with the most recent occurring in California in 2010, initiated by an unvaccinated child who contracted the virus on a family vacation to Europe. He subsequently exposed > 800 people, and 11 other non-vaccinated children also contracted measles.



Image 2-22: Measles, Koplik spots. Small white spots that occur before the rash.



## Quick Quiz

- How is CMV diagnosed in the various patient populations?
- What is the clinical presentation of EBV mononucleosis?
- What are the clinical symptoms of measles?
- What subtypes of influenza A circulated in 2009–2010. Which patient groups suffered the most complications from novel H1N1?
- How do you diagnose influenza A?
- What drugs are recommended for empiric treatment of probable influenza?
- Which patient groups can receive the intranasal influenza vaccine?

## RETROVIRUS

Retroviruses are RNA viruses.

- HTLV-1 causes T-cell leukemia and a neurologic syndrome, **spastic tropical paraparesis** seen in Japan and the Caribbean.
- HTLV-2 causes a rare T-cell variant of hairy cell leukemia.
- HIV-1 causes AIDS (much more on [page 2-48](#)).
- HIV-2, found in West Africa and parts of the U.S., is a virus that causes an illness indistinguishable from AIDS (both HIV-1 and -2 are now picked up by EIA/ELISA). More on HIV on [page 2-42](#).

## RESPIRATORY VIRUSES

### Rhinoviruses

Rhinoviruses are a common cause of URI in adults, usually during the autumn.

### Respiratory Syncytial Virus

RSV infections occur yearly, usually during the autumn and winter. RSV infections are more severe in the infant, occasionally resulting in pneumonia. Only 1% of affected infants are hospitalized. RSV infection has similar morbidity as influenza and especially affects the elderly and those with immunodeficiency. It is now thought to be responsible for up to 25% of excess winter season mortality that was previously attributed solely to influenza.

RSV is also an important pathogen in hematopoietic stem cell transplant recipients and lung transplant recipients.

Diagnose RSV by doing an ELISA test on nasal secretions.

## Influenza

Influenza is still a major cause of death, especially if the patient is > 55 years of age with COPD. Vaccination decreases mortality.

There are 3 types of influenza viruses: influenza A, B, and C. Subtypes of influenza A exist based on their specific **neuraminidase** (N1 and 2) and **hemagglutinin** (H1–3) antigens. A and B cause the yearly epidemics of respiratory illnesses. Influenza C causes very mild, if any, symptoms.

Example: The major circulating influenza A subtypes in 2009–2010 were seasonal H3N2, seasonal H1N1, and **novel** H1N1 (swine flu). The novel H1N1 subtype was especially virulent in the following situations: pregnancy, adults and children < 24 years of age, elderly > 65 years, and immunodeficient states.

Influenza presents as a febrile upper respiratory illness with associated myalgias and pharyngitis. Serious complications include viral pneumonia, bacterial pneumonia, mixed pneumonia, rhabdomyolysis, and encephalitis.

Prevention: Making influenza vaccines is always a gamble. It is unknown what strains will predominate the next year and what genetic mutations can happen in the meantime. The better the antigenic match between this year's strains and next year's, the better the vaccine will work. Efficacy of vaccines has varied in recent years from 10–50%.

The live attenuated (intranasal) vaccine is still available for healthy, **non**-pregnant patients ages 2–49 years.

Diagnose influenza A and B with a **rapid antigen test** using upper respiratory secretions or **PCR** on a nasopharyngeal swab. Viral culture and serology is available but not routinely useful. Polymerase chain reaction testing is available to determine the influenza A subtype, if necessary.

Treatment of influenza: Two classes of drugs have been used to treat influenza. The newer **neuraminidase inhibitors** (**oseltamivir**, **zanamivir**) and the older M2 ion channel inhibitors (amantadine, rimantadine).

**Oseltamivir** and **zanamivir** are used to treat both influenza A and B and are the **preferred** drugs for empiric therapy. If given within 48 hours of onset of symptoms, it decreases duration by 30%. If given within 12 hours, it decreases duration by 50%. It also prevents clinical disease in > 90% of household contacts. During the 2009 H1N1 pandemic, the strain was mostly susceptible to these neuraminidase inhibitors.

Amantadine and rimantadine are older agents that were effective **only** against **influenza A** (no M2 molecules in B). Resistance to these agents is common, but every strain and season is different and somewhat unpredictable.

## Coronavirus

### Usual Coronavirus Infection

Coronavirus is an enveloped **RNA** virus. In its usual form, it is responsible for 3–5% of “common colds.” Coronavirus “colds” are more likely to occur in winter and early spring.

### Severe Acute Respiratory Syndrome (SARS)

Severe Acute Respiratory Syndrome (SARS) is due to SARS-associated coronavirus (SARS-CoV). In November 2002 to July 2003, there were > 8,000 cases worldwide and 916 deaths per the World Health Organization. Patients typically had early “flu-like” symptoms that quickly progressed to severe respiratory distress. The elderly were far more likely to be severely affected.

## POLIO

90% of polio is self-limited. Its onset is characterized by an aseptic meningitis and an **asymmetric**, flaccid paralysis **without** reflexes. It is essentially eliminated in the western hemisphere and developed countries worldwide, but it is still a problem in the developing world, especially India. More in the Neurology section, Book 5.

## RABIES

Rabies is especially found in **bats**, raccoons, skunks, foxes, dogs, cats, and ferrets; but not in squirrels, rats, or any other rodent. Worldwide, the vast majority of rabies is transmitted to humans by dogs. By contrast, in the U.S., 24 of the 25 cases of human rabies that occurred between 1995 and 2006 were from **bats**. Rabies usually presents within 1–3 months after exposure with a viral prodrome followed by encephalitis, a Guillain-Barré mimic, or neuropathic pain +/- sensorimotor deficits. The encephalitis is commonly associated with the classic rabies symptoms of hydrophobia, choking, and delirium.

Preexposure prophylaxis is recommended for cave explorers, veterinarians, animal control workers in endemic areas, and anybody who handles bats—but **not** for hunters, mail carriers, or the average person.

Diagnosis of rabies is accomplished via evaluation of several specimens, including saliva, skin, and brain biopsy, and CSF. Serology is **not** useful.

When a person is bitten by a potentially rabid animal, rabies immune globulin (RIG) and postexposure vaccination may be indicated. Each should be given in a separate site. The immune globulin should be injected in the tissue around the wound. Indications for rabies prophylaxis vary depending on supply. Contact the CDC to determine current recommendations if you believe rabies immune globulin might be necessary. Know that if a person has been previously vaccinated, he needs only a booster after a bite, not immune globulin.

If suspect animals can be captured, a veterinarian should observe dogs, cats, and ferrets for 10 days for signs of rabies. Wild animals should be euthanized and tested for rabies because observation in these animals is unreliable.

## MUMPS

Mumps (**RNA** virus) occurs most commonly in winter and early spring. Although it often is asymptomatic, it can present with uni- or bilateral parotitis, aseptic meningitis, and/or encephalitis. 15–20% of post-pubertal males with mumps get an epididymo-orchitis, which is usually unilateral. Postinfection sterility is a **rare** occurrence. To differentiate mumps from bacterial parotitis, just check a Gram stain of the parotid secretions. There are many WBCs and organisms in bacterial parotitis and **none** in mumps. Another cause of enlarged parotid glands is frequent vomiting. Always consider bulimia in an adolescent or adult with parotid gland enlargement.

## PARVOVIRUS

Parvovirus is a small **DNA** virus. One parvovirus, B19, causes various disorders, ranging from **erythema infectiosum** (“**Fifth disease**”) to arthralgias/arthritis to aplastic anemia. Erythema infectiosum is a mildly contagious, self-limited infection that causes a rash and arthritis. The facial component of the rash causes a “slapped cheek” appearance. This rash is much more common in children, and the arthritis is more common in adults. In patients with chronic hemolytic anemias or AIDS, it can cause a pure red cell aplasia, termed “**aplastic crisis**”—recognize this is different from aplastic anemia. In these patients, the bone marrow shows characteristic “giant pronormoblasts.” Diagnosis can be made with serology, assessing acute and convalescent IgG and IgM titers. Look for a 4-fold rise in titer. Alternatively, PCR on peripheral blood can be performed.

## ARBOVIRUSES

Arboviruses are mainly transmitted by mosquitoes or ticks. Various arboviruses occur in the U.S., typically in the late spring and summer. Until recently, most cases occurred along the Gulf Coast in Louisiana and Florida. Now, with West Nile virus, the arboviruses are seen from coast to coast. Today, West Nile virus is the most commonly identified arbovirus.

Besides West Nile, La Crosse, St. Louis, Eastern Equine (EEE), Western Equine (WEE), Venezuelan Equine, Powassan, and Colorado tick fever viruses occur on occasion in the U.S. Almost all of these have similar symptoms: fever, headache, chills, and varied severity of encephalitis or aseptic meningitis. However, many cases are asymptomatic; only about 1/150 of infected patients present with symptoms.

Diagnosis: finding virus-specific IgM antibody in the CSF or serum.



## Quick Quiz

- Name some animals that transmit rabies.
- What are complications of mumps in the male?
- Which virus is associated with the "slapped cheek" rash?
- What does the bone marrow show in patients with pure red cell aplasia from parvo B19?
- How is West Nile virus encephalitis diagnosed?
- Characterize a patient with hantavirus pulmonary syndrome.
- When does Dengue hemorrhagic fever develop?
- Which HPV types are associated with cervical cancer?
- What causes PML, and how does it present?

## HANTAVIRUS

A hantavirus-associated disease, called Hantavirus Pulmonary Syndrome (HPS), starts with severe myalgias, fever, headache, and cough—and quickly progresses to ARDS and death. More than 50% die. The primary reservoir in the U.S. is the deer mouse. On the Eastern coast and in the Southeast, the cotton rat is the main reservoir. The infection occurs when the excreta or saliva are inhaled. Transfer of the virus can also occur through broken skin. No person-to-person transfer is known to have occurred.

Symptoms:

- **Early:** constitutional symptoms in all. About 1/2 have N/V, diarrhea, and abdominal pain.
- **Late:** 4–10 days later—coughing and shortness of breath as ARDS develops.

**No rash.** The clue: a young person with severe hemorrhagic pneumonia with decreased platelets and increased hematocrit.

## DENGUE FEVER

Dengue fever, dengue hemorrhagic fever, and dengue shock syndrome are caused by any of 4 serotypes of the flavivirus. It is a tropical disease that uses humans and the day-biting *Aedes* mosquitoes (*Anopheles* carry malaria) in its life cycle. Dengue fever has had resurgence in South America and Mexico, with a few cases in South Texas. 2009 and 2010 were remarkable years for a Dengue outbreak within the continental United States, with cases acquired locally in the Florida Keys. **No vaccine** is available yet.

Symptoms: rapid onset of high fever; severe myalgias, and arthralgias ("breakbone fever"); and severe headaches with N/V, followed by a macular red rash that

covers most of the body. A second rash that looks more like measles occurs later, along with a recurrence of fever ("saddleback fever"—up, down, up). Dengue is diagnosed by measuring a **serum IgM** level.

Suspect this in a traveler with these symptoms who has returned from tropical latitudes (including the Caribbean and Mexico). Treatment is **supportive**.

When a patient who has had the above clinical syndrome (dengue fever) is exposed to a different serotype, dengue hemorrhagic fever can develop. Patients present with fever, shock, thrombocytopenia, and may have spontaneous bleeding.

## SLOW VIRUSES

### Overview

There are 2 classes of slow viruses:

- 1) Normal viruses such as papilloma (warts) and polyomavirus (PML)
- 2) Defective viruses, such as the defective measles virus, which cause subacute sclerosing panencephalitis

### Papillomavirus

Papillomavirus causes warts. All warts tend to recur.

Genital warts are associated with an increased risk of cervical cancer. There are many variants, and 15 of these variants found worldwide are designated high risk for cervical cancer. HPV **16** and **18** are the most common causes of **cervical cancer** (60% and 10% respectively). The strains that cause cervical cancer are **usually subclinical**! Much more on cervical cancer in the Oncology section, Book 4.

HPV 6 and 11 are the most common causes of the exophytic, grossly visible genital warts. HPV 6 and 11 carry **little risk** for cervical cancer.

HPV 1, 2, and 5 are common causes of plantar warts.

### Polyomavirus JC

Reactivation of the JC virus in the immunosuppressed host, usually HIV/AIDS and CD4 < 200, results in progressive multifocal leukoencephalopathy (**PML**), which is due to progressive demyelination of the white matter. PML, because it is multifocal, has varied presentations. Usually, the patient suffers altered mental status, followed by various focal motor/sensory deficits. Suspect PML by observing multifocal, demyelinating lesions in the white matter on MRI.

Diagnosis can be made via histopathology of brain tissue. The JC virus can also be identified in the CSF using PCR—sensitivity is 70–90%.

### Subacute Sclerosing Panencephalitis (SSPE)

Subacute Sclerosing Panencephalitis (SSPE) is a rare form of encephalopathy thought to be due to a **measles** virus that had been changed, but not eradicated, by the immune reaction to the primary infection. Occurrence is 1/300,000 cases of measles. Patients usually had measles at an age of < 2 years and present with dementia, myoclonus, and new-onset seizures ~7–10 years after the initial infection. Most die within several months of onset.

### PRION DISEASE

Prions are proteinaceous infectious particles that lack nucleic acid and constitute a previously unknown means of transmitting disease.

Prion diseases include Kuru, Creutzfeldt-Jakob disease (CJD), variant of CJD (vCJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, and fatal familial insomnia. In animals, prions cause scrapie and mad cow disease (= bovine spongiform encephalopathy = vCJD when transmitted to humans).

Human prion diseases can be sporadic (CJD), infectious (vCJD, kuru, rare cases of CJD), or genetic (GSS syndrome, familial CJD, fatal familial insomnia).

Kuru is found in New Guinea, is associated with cannibalism, and is thought to be transmitted by ingestion of raw human brain tissue. It has an incubation period of up to 30 years. No new cases since ritual cannibalism stopped.

Creutzfeldt-Jakob disease (CJD) is the most common prion disease. It is almost always sporadic but ~ 5% are infectious (e.g., corneal transplants, cadaveric human growth hormone), and very few are genetic. Its incubation period is ~ 18 months. Patients with CJD get myoclonus and severe dementia. Neurologic symptoms predominate. They generally die within 5 months! There is no effective therapy for either kuru or CJD. The EEG is diagnostic.

A variant of CJD (vCJD), probably transmitted from beef with bovine spongiform encephalopathy (BSE, **mad cow disease**), has been contracted worldwide, with most cases in the United Kingdom. No endemic U.S. human cases of vCJD have been reported, although a small number of cows, originally from Alberta, Canada, were “found down” and determined to be infected. The only U.S. human cases so far were people who had moved from England. Canada, however, has since been deemed a “minimal risk region” for BSE. This change in status for Canada has reduced importing of Canadian beef.

vCJD patients have early-on psychiatric symptoms and late-appearing neurologic symptoms (~ 6 months, ataxia). Once neurologic symptoms appear, progression to death is rapid. Exams: Look for a young adult from England with progressive psychiatric symptoms and ataxia.

## HIV AND AIDS

### OVERVIEW

Changes in the treatment and management of HIV infection are evolving rapidly. The following covers the basics—not the cutting edge. Antiretroviral drugs are listed in the content specifications for the exams, so this information is presented here. However, realize that the Boards are more likely to focus on diagnosis and complications of disease and side effects of medications than on having you start or change antiretroviral treatment (**ART**) regimens.

### HIV STRUCTURE

The HIV particle is composed of a dense, single-strand **RNA** core surrounded by a lipoprotein envelope. The RNA contains reverse transcriptase, which allows the RNA to be transcribed into DNA, which is then assimilated into the host's genome. The cell then becomes an HIV-producing machine.

The structure in the lipoprotein envelope that allows the HIV to attach to the **CD4+** T cell is named **gp120**. As opposed to influenza, the envelope on HIV is very unstable; therefore, it is much more difficult to make a vaccine against it.

### HOW HIV INFECTS

HIV gp120 envelope glycoprotein binds to the CD4 receptors and coreceptors (such as CCR5) on the **helper** T cells, macrophages, and monocytes. The virus must bind to both the CD4 and CCR5 molecule to fuse with the cell. After fusion, the viral core material enters the cell. Immune dysfunction results from the ongoing destruction of CD4 cells. The CD4 cells are the major regulator cells in the body; they suppress B lymphocytes and regulate the CD8 suppressor cells.

With the decrease in CD4+ counts, B cells become **deregulated** and are no longer suppressed, causing a polyclonal **increase** in total serum immunoglobulins, even though overall antibody **function** is **decreased**! For this reason, infectious diseases in AIDS patients include not only the **cell-mediated** infections (PCP, viruses, mycobacteria, and fungi), but also those seen with **humoral deficiency** (pneumococcus, meningococcus, *H. influenzae*, and *Giardia*).

### EPIDEMIOLOGY

The latest U.S. statistics are from 2009 and represent 2006–2009. The numbers given are estimates made by the CDC, based on a statistical analysis that corrects for reporting delays and missing risk factor information.



## Quick Quiz

- Patients with HIV/AIDS are at risk for developing infections with what organisms?
- How is HIV infection diagnosed? What is the utility of measuring HIV DNA?
- What is the viral set point, and what is its significance?

### Relevant epidemiology:

- New diagnoses of HIV in 2009 = 42,793 (!)
- Age group with the highest rate of infection = 40–44 years.
- Race/ethnicity with the highest rate of infection = blacks/African-Americans (49%). Rates in Caucasians remained stable.
- The transmission category with the greatest number of new diagnoses was male-to-male sexual contact = 61% of all new diagnoses. These numbers have increased.
- Heterosexual transmission represented 27% of all new diagnoses.
- Injection drug use accounted for 9% of cases.

## DIAGNOSIS

HIV **infection** is diagnosed by demonstrating the presence of the virus or antibody to the virus.

The standard screening test for HIV is an enzyme immunoassay (EIA). This test detects antibody to the virus and is 99% sensitive and 90% specific. Positive responders are confirmed by the Western blot. Antibody to HIV is usually detectable 6–12 weeks after inoculation.

Note that the enzyme-linked immunosorbent assay (ELISA) and the enzyme immune assay (EIA) are two very similar tests that were developed independently and simultaneously and measure the same thing. The terms are often used interchangeably but, with HIV testing, EIA is the more correct term.

Viral antigens can be assessed with tests that measure the actual levels of HIV RNA (**viral load**) by amplifying the RNA. The main use for determining the level of HIV RNA (viral load) is to **monitor response** to ART (antiretroviral therapy). Disadvantages of its use as a tool to diagnose HIV include cost and time. However, it may have a role in some clinical situations such as acute infection, indeterminate results of serologic testing, and neonatal infection.

A number of **rapid** tests are available which assay blood, serum, plasma, or saliva. Many are able to provide results in less than 30 minutes. Positive tests must be confirmed with EIA and Western blot tests. Fourth generation assays are available in some labs, which detect antibodies and p24 antigen simultaneously; however, these are not presently widely available in clinical labs.

Again:

- 1) EIA for HIV **antibody** is the usual means of determining HIV infection. A positive test is confirmed by Western blot.
- 2) HIV RNA test determines **actual RNA levels** or “**viral load**,” which may be undetectable in a person under treatment for HIV infection.

After initial infection, the virus replicates quickly and robustly, until the body controls the infection with cell-mediated immunity. The body will establish a kind of homeostasis with the virus, where the virus will be contained to some degree; however, the body will not contain the virus entirely (e.g., viral load of zero). Some people will contain their virus better than others.

The viral **set point** is that **viral load** which is established after a patient's immune system **controls** primary infection, and it varies from person to person. When a patient stops ART (antiretroviral treatment), his virus typically rebounds to a level that is at least as high as his set point.

## TREATMENT OF HIV INFECTION

Combination ART is the **standard of care**.

When to start treatment is easy (2012): start ART on **all** treatment-naïve HIV patients (discussed more under When to Initiate ... on [page 2-47](#)).

What type of regimen is a tougher decision. Many factors are involved and the major ones will be reviewed.

Adherence to the ART regimen is a key determinant in the degree and duration of viral suppression. It is **extremely** important to actively involve the patient in the treatment decision-making process. Guide decisions regarding initiation or changes in ART by monitoring plasma HIV RNA (viral load) and CD4 T-cell counts, in addition to the patient's clinical condition. The effectiveness of all drugs decreases if drugs are used in regimens that are not fully suppressive due to development of resistant mutations. All treatment decisions should be based on treatment guidelines offered by the NIH or by the HIV Medicine Association (created by IDSA). Both of these guidelines are released yearly and are posted on the Web. Know that treatment options are always evolving in HIV disease.

First, we will review the major classes of anti-HIV drugs, then the treatment protocols. To get a good understanding of how these drugs work, refer frequently to the earlier paragraphs on HIV Structure and How HIV Infects as you go through the different classes of anti-HIV drugs.

Even though this is fun and good to learn, for Board questions regarding HIV treatment, you mainly need to know:

- when to initiate treatment ([page 2-47](#))
- the main treatment protocols ([page 2-47](#)), and
- the main side effects (see the Quick Quiz on [page 2-45](#) and see [page 2-46](#)).

## Antiretroviral Drugs

Drug acronyms for the major classes of anti-HIV drugs:

- 1) NRTIs = Nucleoside Reverse Transcriptase Inhibitors and Nucleotide Reverse Transcriptase Inhibitors
- 2) NNRTIs = Nonnucleoside Reverse Transcriptase Inhibitors
- 3) PIs = Protease Inhibitors
- 4) FI = Entry/Fusion Inhibitor
- 5) Integrase inhibitors

### NRTIs

#### Nucleoside Reverse Transcriptase Inhibitors

These drugs are analogs of the deoxynucleotides needed to synthesize viral DNA. They inhibit the replication of HIV by competing with the normal deoxynucleotides. When a NRTI is **incorporated into** the growing viral DNA, the growing chain terminates and that DNA cannot then be incorporated into the cell's DNA and produce more HIV. Note that nucleotide RTIs work the same way (see below) and the term "NRTI" covers both.

**Zidovudine (ZDV)** = azidothymidine (AZT) = Retrovir®. This is the oldest of the antiretroviral drugs but still remains very useful, especially in the settings of resistant virus or pregnancy. ZDV is **well tolerated** at currently used doses, but it causes bone marrow suppression (anemia, granulocytopenia) and myopathy. A **macrocytosis** (elevated MCV) always occurs but has no clinical consequence. ZDV does **not** usually cause problems for the kidneys or lungs and does **not** cause pancreatitis. ZDV is associated with lipodystrophy when taken chronically.

Currently, ZDV is only rarely used as initial therapy. Some patients, who have been on treatment for a long period of time, remain on ZDV usually in combination with 3TC.

**Lamivudine (3TC, Epivir®)** is a very effective drug, and it is well tolerated. 3TC has been the most commonly prescribed antiretroviral agent. Side effects are **rare**.

**Emtricitabine (FTC, Emtriva®, Coviracil®)** is a drug that is extremely effective. It has minimal toxicity. FTC is an analog of 3TC and exhibits **complete cross-resistance** (i.e., if patients have resistance to 3TC, they have resistance to FTC). It is used in **all** the recommended combinations for ART-naïve patients.

**Abacavir (Ziagen®)** is very effective. The most serious reaction is a **hypersensitivity** reaction, which usually occurs within 4 weeks. The reaction consists of a generalized rash and/or a flu-like illness with fever, chills, N/V, myalgias, cough, and shortness of breath. In patients with this hypersensitivity reaction, a rechallenge with abacavir (after discontinuation of the drug) causes an accelerated

hypersensitivity reaction that causes multiple organ failure which can be rapidly fatal.

Abacavir hypersensitivity is linked to the *HLA B-57:01* gene, and now it is recommended that all patients be tested for this gene before beginning abacavir therapy. If negative, the hypersensitivity rate decreases to < 2%.

Rarely used:

**ddI** (didanosine, Videx®): This is now less commonly used due to toxicity. The most severe side effects are pancreatitis (which can be life-threatening) and peripheral neuropathy. ddI is also associated with lipodystrophy, mitochondrial toxicity, and low CD4 counts (even with a suppressed viral load). Fatal lactic acidosis can occur with concomitant use of d4T. It should not be used with d4T.

**d4T** (stavudine, Zerit®): d4T is now used only in salvage therapy because of toxicity. d4T can cause **lipodystrophy and mitochondrial toxicity** syndromes. Side effects include pancreatitis and peripheral neuropathy. Also, d4T in combination with **ddI** can cause a **fatal lactic acidosis**—especially in pregnant women. This combination of d4T and ddI is basically used only for salvage regimens in the U.S.

#### Nucleotide Reverse Transcriptase Inhibitors

**Tenofovir (TDF; Viread®)** is a nucleotide-RTI very similar to the above nucleoside analogs, except that nucleotide RTIs are chemically pre-activated and, therefore, require less biochemical processing than the nucleoside RTIs.

Tenofovir has once-daily dosing and a good side-effect profile—mainly asthenia/headache/N/V/D/flatulence. Azotemia and a Fanconi-like syndrome have been seen with tenofovir, particularly in patients predisposed to renal disease.

### NRTI Combos

NRTI combinations:

- Combivir® (3TC/ZDV)
- Trizivir® (3TC/ZDV/abacavir)
- Epzicom® (3TC/abacavir)
- Truvada® (TDF/FTC)
- Atripla® (TDF/FTC/efavirenz)
- Complera® (TDF/FTC/rilpivirine)

Know that the two drugs, **TDF** and **FTC**, are included in all recommended combinations for initial treatment of ART-naïve patients.

Do not use ZDV and d4T together due to antagonism. Avoid the combination of tenofovir and **ddI** because of drug interactions and intracellular accumulation of metabolites that can actually cause T-lymphocyte levels to drop.



## Quick Quiz

- What are side effects of ZDV? ddI? d4T?
- What are serious side effects of abacavir?
- Which NRTI can be associated with development of kidney disease?
- What is the primary toxicity of nevirapine?
- Which antiretroviral is teratogenic?
- What metabolic defects have been associated with use of protease inhibitors?
- Which PI is used to boost the drug concentrations of other PIs?
- Which PI is associated with kidney stones?
- Which drug is associated with indirect hyperbilirubinemia?

### NNRTIs

Nonnucleoside RTIs work very differently from the NRTIs. These make the reverse transcriptase ineffective by **binding** to another site on the enzyme.

**Nevirapine** (Viramune®) is the first of this class of drugs. Rash, which can be severe, is the primary toxicity. Fatal hepatic toxicity, especially in women with CD4 count > 250 and in patients coinfecting with hepatitis, has been reported.

**Efavirenz** (EFV, Sustiva®) is effective and commonly used. However, it is associated with teratogenicity, is **absolutely contraindicated in pregnancy**, and is **discouraged** from use in women of **child-bearing potential**. Other side effects include rash, vivid dreams, insomnia, fuzzy thinking, and mood swings. A fixed-dose coformulation with TDF/FTC is available (Atripla®).

**Etravirine** (Intelence®) was approved in 2008. Monitor for serious skin rash. It is useful in HIV infection that has been previously resistant to the other NNRTIs.

**Rilpivirine** (Edurant®) is a new NNRTI just released for use in naïve patients. A fixed combination with TDF/FTC is available (Complera®).

### PIs

**HIV protease inhibitors**—PIs (ataza-, daru-, rito-, lopi-, fosampre-, saqui-, indi-, nelfi-, tipranavir) inhibit the HIV protease enzyme that is involved with processing the final assembly of the virion. Except for nelfinavir, all PIs are given with low-dose **ritonavir** because ritonavir boosts the drug levels of the coadministered PI (termed “ritonavir boosting”).

**Atazanavir** and **darunavir** are the most commonly used protease inhibitors currently. Lopinavir is less commonly used due to side effects, but remains useful in setting of pregnancy and for those patients who tolerate it well. Tipranavir is used only very rarely for highly resistant

virus not sensitive to other PIs. Fosamprenavir is sometimes used because of its flexibility of dosing and lack of drug interactions.

Fat redistribution, lipid abnormalities (increased triglycerides and cholesterol), new-onset Type 2 diabetes, and osteoporosis have been recognized with the use of PIs. However, in treating the lipid abnormalities, do **not** use simvastatin or lovastatin with any of the PIs! Also avoid other drugs that cause interactions: rifampin, astemizole, cisapride, and St. John's wort.

**Atazanavir** (Reyataz®) is a once-daily PI that doesn't have adverse lipid effects. For maximum potency, the drug needs to be boosted with ritonavir. It is associated with unconjugated (indirect) hyperbilirubinemia of **no** clinical consequence.

**Darunavir** (Prezista®) was approved in 2006. Monitor use closely in patients with underlying hepatitis coinfection. Currently, darunavir is used in all lines of therapy from naïve to salvage. It can be used qd or bid and is better tolerated than Kaletra® (see 2 down).

**Ritonavir** (usually shown as “/r” in its low-dose boosting role, Norvir®) is now mainly used in low doses to **boost** the levels of most other PIs. It is a potent drug, but **patient tolerability is poor** due to side effects. The main side effects are N/V, flushing, distorted taste, and paresthesias. There are many drug interactions because of interference with the p450 enzyme system.

**Lopinavir/ritonavir** (LPV/r; Kaletra®) is a coformulation of lopinavir and low-dose ritonavir. Lopinavir is available only in this coformulation. It is **very potent** and well tolerated. Currently, it is not generally used for initial therapy because it is less well tolerated than atazanavir or darunavir and causes more lipid abnormalities.

**Fosamprenavir** (Lexiva®) is the prodrug of amprenavir. It requires fewer pills and eliminates the major side effects of amprenavir. Primarily used because of lack of drug interactions and flexibility of qd or bid dosing.

Rarely used :

**Saquinavir** is not used much, having been replaced by newer, simpler PIs. In 2010, the FDA added a warning that ritonavir-boosted saquinavir has been associated with prolongation of the QT interval and development of *torsade de pointes*. Do an ECG before prescribing, and do not give the regimen to any patient with a QT interval > 450 ms. Also, recheck the ECG after 2 weeks for new prescriptions.

**Indinavir** (Crixivan®) has side effects that include an asymptomatic hyperbilirubinemia and a high incidence of **nephrolithiasis**. Indinavir is rarely used because of the development of PIs that are less toxic and have more convenient dosing.

**Nelfinavir** (Viracept®) side effects include **diarrhea and rash**. It is less commonly used because of the GI intolerance and the better efficacy of the newer PIs. Nelfinavir is the only PI that is not boosted with ritonavir.

**Tipranavir** (Aptivus®) was approved in late 2005. It has adverse lipid effects, and its main side effects are GI-related and rash. Used only rarely for extremely resistant virus.

### Entry / Fusion Inhibitors

**Maraviroc** (Selzentry®) is the first drug approved for treatment of CCR5-tropic HIV—which are the strains of HIV that appear early in the disease. A coreceptor tropism assay to confirm these strains should be performed prior to use of maraviroc. Maraviroc **blocks** the process by which these CCR5-tropic HIV virions **enter** CD4+ cells. It is an **oral** agent and carries an FDA boxed warning for drug-induced **hepatitis**. Maraviroc is approved for use in combination therapy in all lines of therapy, including naïve patients. It is generally well tolerated.

**Enfuvirtide** (Fuzeon®) is the only fusion inhibitor available. These also **prevent entry** of an HIV virion into the CD4+ cell. Given by subcutaneous injection, its main side effects are local reactions at the injection site and increased risk of bacterial pneumonia. It is not part of most regimens because it requires injection and is used only for **salvage** treatment.

### Integrase Inhibitors

**Raltegravir** (Isentress®) is the only integrase strand transfer inhibitor (**INSTI**) currently available. It prevents the HIV integrase enzyme from inserting HIV's genetic information into an infected cell's own DNA, halting this critical step in the life cycle of HIV. It is an **oral** agent. Raltegravir is now indicated for **all** lines of therapy, including naïve patients. Its twice-daily dosing is well tolerated with few drug interactions and no effect on lipids.

### Key Words and Side Effects

Key word/phrases to remember for side effects:

- NRTIs
  - ZDV: bone marrow suppression and myopathy
  - Abacavir: potentially fatal hypersensitivity reaction
  - The “Ds” (ddI and d4T): pancreatitis, peripheral neuropathy, mitochondrial toxicity (lipodystrophy)
  - Tenofovir: acute kidney injury with possible renal failure
- NNRTIs
  - Nevirapine: rash
  - Efavirenz: teratogenic; CNS side effects (bad dreams)
- PIs:
  - All PIs: lipodystrophy, hyperlipidemia (except atazanavir), Type 2 diabetes, osteoporosis
  - Atazanavir: indirect hyperbilirubinemia
  - Indinavir: kidney stones
  - Boosted saquinavir: prolonged QT
  - Nelfinavir: diarrhea

## State of Current Treatment

### Overview

Again, **combination ART** is the **standard of care**. Many factors go into the choice of when to start ART and which regimen to choose. Patients should understand the risks and benefits of therapy, that treatment regimens are presently lifelong, and the importance of adherence. Selection of an ART regimen for an individual patient should be based on many factors including: efficacy, side effects, dosing frequency, pill burden, comorbidities, and drug interactions. The goal of ART is **undetectable HIV-1 RNA**.

HIV RNA **assays** are available for accurately determining viral load. Prior to the availability of these assays, most believed the HIV virus entered a prolonged latency period until the onset of symptoms. It turns out that there is continuous replication from the onset of infection to death. Now we know that we do not eradicate the HIV virus even in people with undetectable viral loads on ART. The virus remains in “**reservoirs**,” although we do not fully understand where all the reservoirs are. Long-lived memory T cells seem to be an important site of reservoir virus.

The CD4 T helper lymphocytes are the principal cells targeted by reproducing HIV virions. Tremendous and continuous **CD4 lymphocyte destruction**—eventually causing decreased levels—occurs after HIV infection. **CD4 levels** are a good indicator of disease severity, viral load, and level of immunity.

Know the following regarding HIV treatment:

- Remember that CD4 count is **no longer used** to determine when to **start** ART therapy. ART therapy is now recommended for **all** patients with HIV infection.
- **Always** use combination therapy for HIV. Combination therapy decreases serum viral load—sometimes tremendously—for prolonged periods. Given to patients with HIV disease and evidence of immunologic compromise (**low CD4 counts**), combination therapy prolongs survival and decreases AIDS-associated opportunistic infections.
- The degree of **decrease in viral load** induced by combination ART has a good predictive value.

### Indications for Using Drug-Resistance Assays

Resistance testing is now a standard of care and recommended for those:

- **initially** presenting for HIV care,
- who may be developing **drug resistance**, or
- who are **pregnant**.

It is indicated for treatment-naïve patients immediately **before** initiating treatment; e.g., if ART is deferred, resistance testing should also be deferred and done just before initiation of ART.



## Quick Quiz

- What is the best predictor of long-term outcome in the patient infected with HIV?
- Which new HIV+ patients should receive resistance testing?
- Below what CD4 count is initiation of ART recommended?
- Which exposures should not receive PEP for HIV?
- Which pregnant women should be treated for HIV? With what? What is the treatment goal?

Currently, **2 types of resistance testing** are available—genotypic and phenotypic. Either or both can be used in the setting of increased viral load with presumed HIV-resistance to help determine change in therapy. If resistance is determined, then you can switch from ineffective drugs to ones that are theoretically effective.

The **genotype** test will detect specific genes in the individual patient's HIV virus known to confer resistance toward a specific antiretroviral drug. It is a cheaper and faster test; it also gives more information. As such, it is recommended over the phenotype.

The **phenotype** test determines if the gene is operating and resistance is being expressed. This is sort of like a crude antibiogram for the HIV virus. This phenotype test becomes more useful as the number of mutations increases and as the interpretation of genotypes becomes more difficult and less reliable.

### When to Initiate Antiretroviral Therapy (ART)

The following is the newer (and much more simplified) guideline regarding when to initiate therapy for treatment-naïve patients based on the Panel on Antiretroviral Guidelines for Adults and Adolescents (2012).

**Start treatment without delay for all HIV-infected patients!** See, this really is easier. Strength of this recommendation for increasing CD4 counts and some coincident conditions:

- CD4 < 350 or AIDS-defining illness (AI)
- CD4 350–500 (AII)
- CD4 > 500 (AIII)
- Pregnancy (AI)
- AIDS-defining illness (AI)
- HIV-associated nephropathy (AII)
- HIV/HBV coinfection (AII)

Note that these guidelines changed to be all-inclusive in 2012. The thinking here is that earlier treatment may preserve cellular immune function longer and establish a lower viral set point.

### Which Combination of Drugs to Use

The following recommendations come from the DHHS 2012 treatment guidelines.

Preferred initial regimens for antiretroviral-naïve patients (after resistance testing):

- Tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) (AI)
- Tenofovir/emtricitabine/ritonavir-boosted atazanavir (TDF/FTC/ATV/r) (AI)
- Tenofovir/emtricitabine/ritonavir-boosted darunavir (TDF/FTC/DRV/r) (AI)
- Tenofovir/emtricitabine/raltegravir (TDF/FTC/RAL) (AI)

To make this easier, just remember **TDF/FTC** (tenofovir/emtricitabine) is in **all** regimens and add efavirenz, boosted atazanavir/darunavir, or raltegravir.

Remember: **EFV** (efavirenz) is **absolutely contraindicated in pregnancy** and also should not be given to women trying to get pregnant.

### When to Change HIV Therapy

Again, this is controversial. However, 2 things to know:

- 1) Do not change drugs based on one viral load result.
- 2) Intolerance to the medication should prompt an evaluation for change of therapy.

### Post-Exposure Prophylaxis (PEP)

First, recommend cleaning the site of exposure with water and soap, if applicable. Determine the exposure risk: Was the source material blood or bloody fluid? If so, then determine if it was a percutaneous exposure (yes—PEP recommended), or mucous membrane or skin with compromised integrity (PEP probably recommended). It is easier (and frequently asked on exams) to remember to whom **not** to give PEP: Do **not** give PEP for intact skin exposures and urine-source exposures.

When PEP is indicated, use **potent combination therapy**. Treatment should be started ASAP—within hours of exposure—and be continued for **4 weeks**. HIV testing is recommended at 0, 6, and 12 weeks, and 6 months after the exposure.

### Pregnancy and ART Therapy

A primary consideration is that suppressing the viral load in the mother lowers the risk of transmission to the newborn.

Treat **all** pregnant, HIV-infected women with ART regardless of CD4 level or viral load. The goal is to make her viral load **undetectable**. Always do resistance testing if able (i.e., viral load > 500–1,000 copies/mL).

Note the following commonly used ART drugs to **avoid** in pregnant women:

- **Efavirenz** (EFV) due to association with teratogenicity.
- **Nevirapine** (NVP) is not recommended for women with CD4 counts > 250, and caution is advised for use in any pregnant woman.

Preferred therapy for **ART-naïve** pregnant women is ZDV/lamivudine + lopinavir boosted with ritonavir:

ZDV/3TC + LPV/r

Three scenarios:

- 1) If the patient is already on ART and has undetectable virus, continue her current regimen except **avoid** EFV, NVP, and d4T/ddI as discussed above.
- 2) If she is **not** on ART at time of pregnancy, initiate therapy **immediately** if indicated for her health (high viral load/low CD4, etc.). If she is ART-naïve, give the same ART therapy as above: ZDV/3TC + LPV/r. Therapy can be started before resistance testing results are back—especially if she is in the 3<sup>rd</sup> trimester.
- 3) If the patient is requiring ART solely to prevent transmission to the child but does not meet the other criteria for starting ART therapy, you may wait until the start of the 2<sup>nd</sup> **trimester** to start ART therapy. This will minimize teratogenic effects. Same therapy and considerations as in scenario 2.

So notice that the **same therapy** is recommended to **ART-naïve pregnant women** whether they need it for their health or solely to prevent transmission to the child.

If she is **not** ART-naïve, use past ART history and do resistance testing to determine the best course.

Again, no EFV and probably no NVP, especially if her CD4 count is > 250!

### Labor and Delivery

**All** pregnant women should be given ZDV as a continuous infusion during labor in addition to their current ART therapy.

C-section is recommended if viral load > 1,000 copies at 38-weeks gestation.

**Infants** born to HIV-infected mothers should receive ZDV for **6 weeks** starting within 6–12 hours of birth.

## PRIMARY HIV INFECTION

Don't forget primary HIV-1 infection, previously termed "acute retroviral syndrome." This is a flu- or mononucleosis-like syndrome that occurs 2–4 weeks after initial infection and lasts 1–2 weeks.

Patients with primary HIV infection present with:

- fever,
- lymphadenopathy,
- pharyngitis,

- rash (usually erythematous maculopapular with lesions on face, trunk, or extremities; can include palms and soles),
- mucocutaneous ulcerations involving the mouth, esophagus or genitals, and
- myalgias/artralgias.

Aseptic meningitis is another presentation of primary HIV infection.

Consider primary HIV infection in any sexually active person or drug user who presents with signs/symptoms of **mononucleosis, scarlet fever, or aseptic meningitis**.

Diagnose with a high plasma RNA viral load or positive p24 antigen. Low viral loads (< 10,000 copies) may be false-positive tests and should be repeated with referral to a provider experienced with HIV. HIV EIA (enzyme immuno assay) antibody test becomes positive at 3–7 weeks after exposure.

Current treatment guidelines recommend that ART should be considered for patients with primary HIV infection.

## HIV / AIDS OPPORTUNISTIC INFECTIONS

### Introduction

Opportunistic infections (OIs) are caused by microorganisms that do not commonly cause disease. However, in the setting of immunosuppression such as HIV/AIDS, these microorganisms are able to 'opportunistically' cause disease. The opportunistic infections a patient is at risk for are associated with the patient's CD4+ cell count.

**Primary** prophylaxis is the term used when prophylaxis is given to a patient with no prior history of the OI. **Secondary** prophylaxis is what is given when the patient has a history of previous treatment for that OI.

Common infections and findings in HIV disease include:

- persistent or recurrent seborrheic dermatitis,
- tinea infections,
- psoriasis,
- molluscum contagiosum,
- folliculitis, and
- mucocutaneous infections (hairy leukoplakia, herpes, oral or vaginal candidiasis).

Hairy leukoplakia is caused by EBV.

Management of OIs follows the 2009 guidelines.

### PJP and HIV

#### Diagnosis

*Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia (PJP, formerly PCP) is the **most common opportunistic** infection in AIDS patients. It is the presenting illness in 50% of AIDS patients.

Presentation of PJP: insidious onset of fever, shortness of breath, and dry cough.



## Quick Quiz

- What are the symptoms of primary HIV infection?
- What level of virus could be a false positive in patients with possible acute HIV infection?
- What is the most common OI in the patient with HIV/AIDS?
- What is the usual CD4 count in the patient with HIV/AIDS who develops PJP?
- How is PJP best diagnosed?
- What ancillary treatment should be given to patients who develop hypoxemia due to PJP?
- When should patients be given primary prophylaxis for PJP?
- What is the treatment duration for latent TB in patients with HIV/AIDS?

Again: PJP usually has an **insidious** onset; if an AIDS patient presents with an **acute** onset of pulmonary symptoms, get a sputum for Gram stain and a C&S, and consider starting empiric treatment for **community-acquired pneumonia**.

Lab: ABGs typically show a pH > 7.40. Hypoxia is common. A-a gradient is commonly increased. PCO<sub>2</sub> is commonly low (from respiratory alkalosis). LDH is elevated (> 400), and liver enzymes are normal. The chest x-ray usually shows a diffuse “batwing” infiltrate, although it may also be lobar or unilateral. Occasionally, the chest x-ray is **normal**.

Patients who are most susceptible to PJP have a CD4 count < 200, so **all** of these patients should receive primary PJP prophylaxis.

The best method of diagnosis is by methenamine **silver stain** of samples taken by bronchoscopy or BAL, although induced sputum is effective in up to 50% in some hospitals. PCR is available in some centers and very sensitive.

### Treatment

Treat **mild** PJP with oral TMP/SMX (best) or atovaquone if unable to tolerate TMP/SMX.

Treat **moderate-to-severe** PJP (P<sub>a</sub>O<sub>2</sub> < 70 or A-a gradient > 35) with:

TMP/SMX x 21 days (PO or IV)

**plus**

oral glucocorticoids taper (start on the 1<sup>st</sup> day).

Alternatives:

- IV pentamidine (Inhaled pentamidine is **not** recommended.)

- Primaquine + clindamycin
- Dapsone + trimethoprim
- Atovaquone alone for mild-to-moderate cases

PJP patients must receive **21 days** of effective therapy.

If there is no response after 1 week, or if severe side effects develop, switch to an alternative regimen.

Remember: Include glucocorticoids (start on the 1<sup>st</sup> day) for any patient with a P<sub>a</sub>O<sub>2</sub> < 70!

### Side Effects

TMP/SMX side effects include neutropenia/leukopenia, skin rash, nausea/vomiting, and, occasionally, fever.

Pentamidine causes neutropenia/leukopenia, fever, nausea, vomiting, and diarrhea. Pentamidine also causes azotemia and renal failure. Recurrent courses of pentamidine destroy the islet cells of the pancreas, causing **hypoglycemia**, which may not be reversible. If a patient treated with pentamidine seizes, check finger-stick glucometer! **Hyperglycemia** may also occur with pentamidine.

Again, both TMP/SMX and pentamidine can cause neutropenia/leukopenia.

For some patients with AIDS, the reactions to either TMP/SMX or pentamidine are intolerable, and you must change the medication.

### Prophylaxis

Start **primary** and **secondary** PJP prophylaxis when CD4 < 200.

Stop **primary** and **secondary** PJP prophylaxis when CD4 > 200 for ≥ 3 months in response to ART.

Give TMP/SMX DS 1/d or 3/wk. If patient cannot tolerate, give dapsone or atovaquone. Atovaquone is more efficacious than dapsone and has a lower incidence of side effects than TMP/SMX but is much more expensive than either. Some patients on TMP/SMX discontinue therapy because of rash.

**Secondary** prophylaxis meds (for those with a history of treated PJP) are the same as those use for primary prophylaxis.

TMP/SMX is also a prophylaxis against **toxoplasmosis**.

### Mycobacteria and HIV

#### Tuberculosis

Tuberculosis is also common in AIDS patients, sometimes without infiltrates, and hardly ever with cavitation. Patients usually respond very well to treatment.

Do a yearly assessment for TB: either a TB skin test or interferon-gamma-releasing assay (IGRA) on all persons who are seropositive for HIV.

Treat a positive PPD (> 5 mm) or +IGRA without signs of disease with **INH** for **9 months**.

Treat active TB in a patient with AIDS with empiric isoniazid, rifampin (or rifabutin), ethambutol, and pyrazinamide x 2 months; then narrow to isoniazid + rifampin (rifabutin) x 4 months, based on isolate susceptibility tests (same as in regular patients, except duration is longer if cavitary or disseminated disease is present). See the Pulmonary Medicine section, Book 2, for more on treatment.

Rifampin may have to be replaced by rifabutin or other drugs in patients with HIV and TB coinfection because of extensive drug interactions. Rifabutin also needs adjustments because of drug interactions.

### MAC

*Mycobacterium avium* complex (MAC, *M. avium-intracellulare*) is a common, usually disseminated infection in patients with AIDS. It causes a wasting syndrome with fever, weight loss, night sweats, lymphadenopathy, +/- severe diarrhea. Treat with clarithromycin and ethambutol +/- rifampin.

Start **primary** prophylaxis for **MAC** with clarithromycin or azithromycin when CD4 < 50. Stop **primary** prophylaxis when CD4 > 100 for ≥ 3 months in response to ART.

**Secondary** prophylaxis is the same as the **treatment** regimen. Stopping secondary prophylaxis for patients with a history of MAC is controversial. Most would stop if CD4 > 100 for 3 months.

### Pulmonary: Other

#### **Cryptococcus**

*Cryptococcus* also involves the **lung** and can be disseminated, **commonly** to the CNS. Diagnose by measuring the crypto antigen in the serum and CSF.

Treat meningitis with amphotericin B (deoxycholate or lipid) + flucytosine x 2 weeks; then follow up with oral fluconazole as consolidation. Adjust the dose for patients with renal insufficiency. Make sure to measure and subsequently monitor the CSF opening pressure.

Treat increased ICP with repeat LPs or shunt.

Do **not** give primary prophylaxis for *Cryptococcus*. Secondary prophylaxis is given with daily fluconazole.

#### **Histoplasma**

In patients with HIV/AIDS, *Histoplasma* either affects the lung or disseminates. (Immunocompetent patients have the **calcified** lung lesions.) It can affect **many** organ systems, including the bone marrow. Think of *Histoplasma* infection when an HIV-positive patient presents with interstitial pneumonia, **palate ulcers**, **splenomegaly**, and **bone marrow suppression**. Patients with a very low CD4 count can present with an acute, fulminant sepsis syndrome.

Diagnosis: Blood cultures are often positive, as is the serum and urine histo antigen, in disseminated disease.

Treat severe infections with **liposomal amphotericin B** (this is one infection where **lipid** is preferred over deoxycholate formulation) x 2 weeks with consolidation using itraconazole. Less severe disease can be treated outpatient with itraconazole. (See [page 2-29](#).)

Primary prophylaxis with itraconazole is considered in endemic areas when the CD4 count < 150.

Secondary prophylaxis is given with daily itraconazole.

#### **Coccidioides**

Again lungs, but it also can disseminate. *Coccidioides* is associated with arthralgias, arthritis, hilar adenopathy, erythema multiforme, and erythema nodosum (similar to sarcoidosis).

Treat mild infections with itraconazole or fluconazole. Severe infections are treated with amphotericin B (deoxycholate or lipid). Fluconazole is preferred for cases of meningitis.

Primary prophylaxis is fluconazole or itraconazole in endemic areas if CD4 < 250.

Secondary prophylaxis is given with daily fluconazole.

#### **Aspergillus**

*Aspergillus* and the zygomycetes (*Rhizopus*, *Mucor*) can cause a necrotizing, **cavitating** pneumonia in AIDS patients. Treat invasive *Aspergillus* with voriconazole or amphotericin.

#### **Pseudomonas**

*Pseudomonas* infections are more prevalent in **granulocytopenic** patients (leukemia, chemotherapy, and post-transplant) than in AIDS patients, although AIDS patients definitely can present with *Pseudomonas*, especially when their CD4 count is < 50. It can present oddly, too, as pneumonias, sinusitis, and idiopathic bacteremia.

#### **CMV**

CMV is frequently cultured or observed in BAL/bronchoscopy samples; only **rarely** is it significant.

### GI and HIV

#### **Candida**

If a patient with AIDS has symptoms of dysphagia, think of *Candida*. Not all *Candida* esophagitis is associated with oral thrush. If the patient does not respond to treatment for *Candida*, consider CMV esophagitis.

Treat **mucosal** *Candida* with oral fluconazole, clotrimazole troches, nystatin suspension, or miconazole mucoadhesive tablets. **Esophageal** candidiasis should be treated with IV fluconazole or itraconazole suspension. **Vulvovaginal** *Candida* can be treated with single-dose fluconazole or a topical antifungal.



## Quick Quiz

- When should patients be given primary prophylaxis for MAC? For crypto? For histo? For cocci?
- How is cryptococcal meningitis diagnosed?
- How do you diagnose histoplasmosis in the patient with HIV/AIDS?
- Severe histoplasmosis is treated with what antifungal?
- Esophagitis that does not respond to fluconazole should cause you to consider what virus?
- Name some of the organisms that can cause chronic diarrhea in a patient with HIV/AIDS?
- What is the typical presentation of CNS toxo?

Prophylaxis is usually not given **unless** patients have severe recurrences. ART is the best long-term management. CMV esophagitis is treated with IV ganciclovir or valganciclovir.

### Diarrhea

Chronic diarrhea in AIDS patients is commonly caused by *Cryptosporidium*, microsporidia (includes *Enterocytozoon bienersi* and *Encephalitozoon intestinalis*), *Cyclospora*, *Isospora belli*, or bacterial pathogens (*Salmonella*, *Shigella*, *Campylobacter*).

Special stains on stool specimens are needed to diagnose *Cryptosporidium* (modified acid-fast), microsporidia (modified trichrome), *Cyclospora* (modified acid-fast), and *Isospora* (modified acid-fast).

There is **no** reliable treatment of cryptosporidiosis except to start ART and increase the CD4 count. Nitazoxanide is an option for patients with substantial symptoms, but may not be effective without concurrent CD increases. *Cyclospora* and *Isospora belli* are treated with TMP/SMX. *Salmonella*, *Shigella*, and *Campylobacter* are treated with ciprofloxacin.

### HCV

Test all HIV-infected patients for HCV. Treat those with combined disease the same as those without. Treatment for both is generally initiated simultaneously but, because of pill burden, overlapping toxicities, and drug interactions, if CD4 > 500, some will hold ART therapy until the completion of the HCV treatment.

### Neuro and HIV

#### Encephalitis

Subacute diffuse encephalitis caused **directly** by HIV is a **common** neurologic problem in patients with AIDS.

### Toxoplasma

*Toxoplasma gondii* is the most common cause of “AIDS-associated, enhancing focal space-occupying lesions,” but the differential diagnosis also includes CNS lymphomas. CT scan shows CNS abscesses due to toxo as **ring-enhancing** lesions. There are usually multiple lesions, but there may be just one. Patients often present with headache and vomiting +/- seizures.

If you see ring-enhancing brain lesions in **any** AIDS patient, consider starting empiric treatment for CNS toxoplasmosis: pyrimethamine + sulfadiazine or clindamycin (if sulfa-allergic) + leucovorin (folinic acid). This treatment is given for at least 6 weeks if you plan to officially treat for toxo.

Primary prophylaxis is indicated in patients with CD4 count < 100/mm<sup>3</sup> and with positive *Toxoplasma gondii* IgG. It is accomplished with the same regimen used for PJP prophylaxis (e.g., TMP/SMX DS 1 daily or 3/wk). Primary prophylaxis for *Toxoplasma* encephalitis can be stopped when the CD4+ cell is > 200 cell/mm<sup>3</sup> for 3 months, similar to PJP primary prophylaxis. It gets more complex in patients who cannot tolerate sulfa. Alternative regimens include a combination of dapsone + pyrimethamine + leucovorin.

Secondary prophylaxis includes slightly lower doses of pyrimethamine + sulfadiazine + leucovorin.

### Syphilis

Syphilis, even if previously treated, may **reactivate** in AIDS patients and cause neurosyphilis. Syphilis is treated the same in AIDS as in non-AIDS. Some experts recommend that you should have a low threshold for evaluating a patient for neurosyphilis with lumbar puncture; however, controversy remains on this issue. CDC guidelines recommend evaluation of CSF if neurological symptoms are present.

### CMV

Eye problems are commonly due to CMV retinitis. (See [page 2-37](#).) CMV retinitis is treated with ganciclovir or valganciclovir. Primary prophylaxis is not given. Secondary prophylaxis is with valganciclovir.

### Kaposi Sarcoma

Kaposi lesions are a neoplasia of blood vessels and are due to human herpesvirus 8. Lesions are heaped up and well localized, often with some surrounding bruising.

### And Again: PJP and MAC Prophylaxis

For both **primary** and **secondary** prophylaxis:

- Start PJP prophylaxis when **CD4 < 200** or **oropharyngeal candidiasis** occurs.
- Start MAC prophylaxis when **CD4 < 50**.
- Stop PJP prophylaxis when **CD4 > 200** for **≥ 3 months** in response to ART.

- Stop MAC prophylaxis when **CD4 > 100** for **≥ 3 months** in response to ART.

Note that some physicians will continue secondary MAC prophylaxis treatment for a longer period of time.

## COMMON ID SYNDROMES

### INFECTIVE ENDOCARDITIS (IE)

#### Overview

The current approach to endocarditis is based on the 2008 update to the 2005 guidelines published by the American Heart Association and endorsed by IDSA.

For treatment purposes, endocarditis is typed as follows: native valve, prosthetic valve, culture-negative, and injection drug user. The previous designations of “acute” and “subacute” are no longer used.

#### Native Valve Endocarditis

Native valve endocarditis is more common on the **left** side of the heart and usually occurs on **regurgitant** AV valves (although it can also occur with VSDs and PDAs). We are also seeing more cases of native valve endocarditis in the elderly. Patients with diabetes who develop endocarditis have increased in-hospital mortality.

The microbiology of endocarditis has changed in recent years. Now *S. aureus* is the most common cause, and viridans streptococci are 2<sup>nd</sup> most common. Know that compared to other etiologies, patients with *S. aureus* endocarditis are more likely to die and develop emboli. Enterococci seem to be the least virulent cause of IE.

#### Prosthetic Valve Endocarditis (PVE)

**Early** PVE (< 2 months) is usually due to **seeding during surgery**. An acute presentation means emergent surgery is necessary. Even with surgery, it still has a **40% mortality**.

**Late** PVE (> 2 months) often invades the annulus, and surgery is required. *S. epidermidis* is the culprit in 55–60% of the cases in the 1<sup>st</sup> year after surgery. If the infecting organism is viridans streptococci, antibiotics alone may cure the prosthetic valve infection. Better success is seen with **porcine** bioprosthesis, as opposed to metal valves.

#### History and Physical Exam

History should focus on potential exposures to **typical** organisms:

- Skin infections
- Dental work
- Genitourinary manipulation or obstruction

- IV catheters
- Injection drug use

Also look for **weird** organisms, especially if blood cultures are negative. (Animal exposures predispose to *Coxiella* and *Bartonella*; *Legionella*; *Tropheryma whippelii*.)

Physical exam may show the following classic stigmata:

- Fever
- Conjunctival hemorrhages
- Petechiae (most common skin finding)
- Splinter hemorrhages
- Janeway lesions (blanching, painless, reddish lesions on hands/feet)
- Osler nodes (painful, purplish lesions on fingers/toes)
- Roth spots (retinal hemorrhage)

Systemic involvement can include neuro deficits (most common cause of death), infarctions of spleen and kidneys, immune-complex glomerulonephritis, and septic pulmonary infarction. Some of the above clinical characteristics are included in the modified Duke Criteria for diagnosis (discussed under Diagnosis, below).

#### Laboratory Evaluation

**Blood cultures** are vital in diagnosing endocarditis of any type, and **3 sets** should be drawn **before** starting empiric antibiotics.

Blood cultures in IE patients are usually **positive** due to the constant level of bacteremia. However, bacterial concentration in the blood is low in IE, so a proper amount of blood should be inoculated into each culture bottle.

Ideally, 3 sets separated by at least 8 hours are drawn from peripheral sites, prior to starting antibiotics. If a patient is unstable, get 3 sets up front from various sites and repeat blood cultures later, after antibiotics are started. For most organisms, it will take some time to clear the blood.

Organisms likely to cause endocarditis **and** grow in culture bottles include: *S. aureus*, viridans streptococci, *S. bovis*, and enterococci. The HACEK organisms are also typical causes of endocarditis, and with current blood culture techniques will usually grow. The “HACEK” organisms are *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* and all are usually sensitive to beta-lactams.

2 positive blood cultures growing 1 of these organisms more than 12 hours apart are considered “significant” in terms of the Duke Criteria.

A single positive blood culture that grows species of *Propionibacterium*, *Corynebacterium*, *Bacillus*, or coagulase-negative staph is usually a **contaminant**, provided that the patient is an immunocompetent host without invasive prosthetic devices. The Duke Criteria



## Quick Quiz

- Which side of the heart is more prone to developing native valve endocarditis?
- What is the usual cause of prosthetic valve endocarditis in the 1<sup>st</sup> year after surgery?
- What are the physical exam signs of endocarditis?
- What type of test is critical in the diagnosis of endocarditis?
- How many sets of blood cultures should be drawn on the patient with suspected endocarditis?
- Which organisms are considered "likely" to cause endocarditis?
- What organisms should be considered as a cause of culture-negative endocarditis?
- If a patient has a high clinical probability of endocarditis, should a negative TTE dissuade you from the diagnosis?
- Which patients should definitely receive a TEE in the evaluation of possible endocarditis?
- What is the negative predictive value of a TEE in a patient with native heart valves?

require at least 3 of 4 bottles (or more) to be positive with these organisms to be considered significant.

Other labs that support a diagnosis of endocarditis include:

- Increased ESR or CRP,
- anemia of chronic disease,
- leukocytosis,
- thrombocytopenia,
- active urine sediment (proteinuria and red cell casts), and
- immune activation evidence (low complement levels, cryoglobulinemia, increased RF titer, and RPR+).

RF positivity is one of the Duke's minor criteria.

Pathology and cultures of valve tissue is sometimes useful to make a diagnosis and is included in the Duke Criteria.

### Culture-Negative Endocarditis

If blood cultures are **negative**, there is no history of pre-culture antibiotic treatment, and the patient has clinical criteria for endocarditis, consider the following:

- Fungi
- Q fever (*Coxiella burnetii*)
- *Legionella*
- *Chlamydia psittaci*
- Nutritionally deficient streptococci

If you alert them, the microbiology lab will hold blood cultures longer when endocarditis is clinically likely. HACEK organisms are sometimes cultured this way. The other organisms are usually diagnosed with serology **or** pathology and culture of the valve. *Coxiella* will rarely grow in blood cultures. If it grows, it is **always** significant and is included as a Duke major criterion.

### Echocardiography

The 2005 AHA guidelines were reevaluated by 2006 American College of Cardiology/AHA guidelines on use of echo to diagnose valvular heart disease. IDSA has endorsed the 2006 ACC/AHA recommendations, which include:

- Only patients with moderate-to-high clinical probability of endocarditis should get echocardiography.
- Transthoracic echo (TTE) has a low sensitivity (but high specificity), so a negative test does **not** exclude a valvular lesion. If clinical suspicion is moderate to high, these patients should progress to transesophageal echo (TEE).
- TEE, as a 1<sup>st</sup> test, is recommended for patients with prosthetic valves and for patients in whom you suspect a perivalvular abscess. Even though it's the best test, be aware that TEE can miss an abscess in a significant number of patients.
- A negative TEE in a patient with **native** valves has a negative predictive value of almost 100%.
- If a patient does **not** have a high clinical probability or a technically limited TTE, then a negative TTE is a definitive study (meaning no further workup with TEE is necessary). To be diagnosed with endocarditis, the patient would have to fulfill the Duke Criteria without the echocardiographic findings (rare).

Some institutions are now using TEE as the 1<sup>st</sup> diagnostic test in patients with *S. aureus* bacteremia. This is an invasive and expensive approach, however. It's also problematic because of the increasing incidence of community-acquired *S. aureus* bacteremia.

Some institutions are also "empirically diagnosing" endocarditis without an echocardiogram in patients with a history of *S. aureus* bacteremia if the patient has a metastatic staph lesion, such as an osteomyelitis. Essentially, the treatment duration is the same, so the assumption is that endocarditis is present. The problem with this empiric approach is that you can miss a visible abscess, embolism, or abnormal valve.

### Diagnosis

#### Modified Duke Criteria

Diagnosis is based on fulfillment of the modified Duke Criteria, which includes clinical, laboratory, and echocardiographic characteristics, regardless of whether a patient has native or prosthetic valves. A structured approach is important and useful because

Table 2-4: Treatment of Bacterial Endocarditis

| Organisms                              | Susceptibility Testing                                     | Drug Regimen                                     | Duration                                                  |
|----------------------------------------|------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------|
| Viridans streptococci, <i>S. bovis</i> | PCN-sensitive                                              | PCN G or ceftriaxone                             | 4 weeks<br>Prosthetic valve = > 4 weeks                   |
|                                        |                                                            | (PCN G or ceftriaxone) + gentamicin              | 2 weeks                                                   |
|                                        |                                                            | Vancomycin (alternative)                         | 4 weeks                                                   |
|                                        | PCN-resistant                                              | Increased dose PCN G                             | 4 weeks                                                   |
| <i>S. aureus</i> or coagulase-negative | Methicillin-susceptible                                    | Nafcillin                                        | 6 weeks<br>Prosthetic valve = add rifampin and gentamicin |
|                                        | Methicillin-resistant                                      | Vancomycin                                       | 6 weeks<br>Prosthetic valve = add rifampin and gentamicin |
| Staph, uncomplicated right-sided       | Methicillin-susceptible                                    | Nafcillin + gentamicin or daptomycin             | 2 weeks                                                   |
| Enterococci                            | PCN-sensitive (depending on amp and vanc susceptibilities) | (PCN G or ampicillin or vancomycin) + gentamicin | 4–6 weeks<br>Prosthetic valve = 6 weeks                   |
|                                        | Ampicillin + PCN G + Vancomycin-resistant                  | Very specialized                                 | Very specialized                                          |
| HACEK                                  |                                                            | Ceftriaxone                                      | 4 weeks<br>Prosthetic valve = 6 weeks                     |

not all patients have positive blood cultures or obvious echocardiographic evidence. Diagnosis is easy when the patient presents with classic signs and symptoms +/- bacteremia, but many patients do not present that way.

**Definite** endocarditis is diagnosed when the patient has any of the following:

- Pathologic evidence of disease
- 2 major clinical criteria
- 1 major clinical criterion + 3 minor clinical criteria
- 5 minor clinical criteria

Pathologic evidence would be visible organisms from a vegetation or valve lesion or a positive culture from the same tissue.

**Possible** endocarditis is diagnosed with 1 major + 1 minor, or 3 minor clinical criteria.

### Major Criteria

With a lot of qualifiers, the major clinical criteria are:

- 1) Positive blood cultures
- 2) Abnormal echocardiogram

Qualifiers for blood cultures:

- To count as a major criterion, organisms grown in culture should be the “typical” ones we described previously (*S. aureus*, viridans strep, *S. bovis*, enterococci, HACEK) from 2 separate cultures at least 12 hours apart.
- Any other organism should be observed in at least 3 or a majority of  $\geq 4$  cultures, drawn from separate sites, with first and last culture drawn at least an hour apart.
- Any 1 blood culture that grows *C. burnetii* is significant. A positive serologic test for *C. burnetii* is also significant (e.g., anti-phase 1 IgG > 1:800).

Qualifiers for echocardiograms. Significant echo findings include **any** of the following:

- An oscillating intracardiac mass visible on a valve or on valve-supporting structures
- An oscillating mass in the path of regurgitant jets
- An oscillating mass on implanted intracardiac devices
- An abscess
- Prosthetic valve dehiscence
- New regurgitation of a valve



## Quick Quiz

- Review and commit to memory the modified Duke criteria. What is required for the definite diagnosis of endocarditis?
- Study Table 2-4 and know the variation on the regimens based on resistance patterns and type of valve (native vs. prosthetic).
- List some complications of endocarditis.

### Minor Criteria

Minor clinical criteria:

- Predisposing condition (valve disease or injection drug use)
- Fever
- Vascular phenomena (arterial emboli, pulmonary infarcts, mycotic aneurysms, stroke, conjunctival hemorrhages, Janeway lesions)
- Immunologic phenomena (acute glomerulonephritis, Osler nodes, Roth spots, +RF)
- Positive blood culture that does not meet a major criterion

### Preferred Treatment of Bacterial Endocarditis

We outline the recommendations from the 2005 AHA guidelines (Table 2-4).

#### Viridans Streptococci and *S. bovis*

Sensitive to PCN: 4 weeks of PCN G or ceftriaxone (2 g/d); if gentamicin is added, can reduce duration to 2 weeks (keep at 4 weeks if there is an abscess). Gentamicin is not recommended for patients with renal insufficiency. Vancomycin can be used x 4 weeks in patients unable to tolerate the beta-lactam, but it is **not** preferred for initial treatment.

If there is some resistance to PCN, the regimen is the same but the dose of PCN G is increased.

Prosthetic valve treatment is generally the same regimen, but the **duration** of treatment is lengthened.

Endocarditis caused by either *S. bovis* bacteremia or *Clostridium septicum* sepsis is directly tied to colon cancer in 10–25% of cases, so conduct GI screening in these patients.

#### Staph without Prosthetics

MSSA + left-sided or right-sided disease with emboli: nafcillin x 6 weeks +/- gentamicin for 3–5 days (if isolate is susceptible). This recommendation was included because of data showing that aminoglycoside synergy sterilized the blood more quickly. However, this recommendation became controversial in 2010 because of data showing that inclusion of the aminoglycoside is

associated with an increase in nephrotoxicity but no other difference in outcome (despite the more rapid blood sterilization). Most experts are **not** including the aminoglycoside to treat staph endocarditis now.

MRSA isolates are treated with **vancomycin** x 6 weeks. Alternatively, **daptomycin** may be used, especially if the vanco MIC is > 1.

MSSA + uncomplicated right-sided disease: nafcillin + gentamicin x 2 weeks; or daptomycin. If the isolate is not gentamicin-susceptible, then the 2-week regimen cannot be used. MRSA isolates are treated x 6 weeks with vancomycin only.

#### Staph with Prosthetics

MSSA/MRSA + prosthetic valve disease: (nafcillin or vancomycin) + rifampin + gentamicin x 6 weeks or longer. Surgery is almost always indicated.

#### Enterococci

Sensitive to PCN: (Ampicillin or PCN G or vancomycin, depending on susceptibility) + gentamicin x 4–6 weeks; PCN G not appropriate if isolate is resistant to PCN.

Prosthetic valve treatment is generally the same regimen, but the duration of treatment is lengthened.

For enterococcal species resistant to ampicillin, PCN G, and vancomycin, treatment is difficult and specialized, utilizing variations of linezolid and imipenem/cilastatin with either ampicillin or ceftriaxone.

#### HACEK Organisms

Treat HACEK organisms with ceftriaxone x 4 weeks. Alternatives include ampicillin-sulbactam or ciprofloxacin. If a prosthetic valve is involved, duration is 6 weeks.

### Complications of Endocarditis

Surgery is often required for endocarditis with:

- Vegetations:
  - Persistent vegetation after one has already embolized
  - Vegetation > 10 mm
  - Vegetation on the anterior mitral leaflet
  - An increasing vegetation size while on antibiotics
  - Persistent emboli while on antibiotics
- Valve dysfunction:
  - Heart failure
  - Valve perforation
  - Rupture
- Perivalvular extension:
  - Fistula
  - Valve dehiscence
  - Heart block
  - Large abscess

Table 2-5: Etiology of Meningitis in the United States

| 0–2 months                                                | %     | 3 mo to 15 years       | %     | Adult                  | %     | Notes on > 60 years                                                             |
|-----------------------------------------------------------|-------|------------------------|-------|------------------------|-------|---------------------------------------------------------------------------------|
| <b>Gram-neg</b><br>( <i>E. coli</i> & <i>Klebsiella</i> ) | 20–30 | <i>S. pneumoniae</i>   | 30–50 | <i>S. pneumoniae</i>   | 30–50 | <i>S. pneumoniae</i><br><i>N. meningitidis</i>                                  |
| <b>Strep (Group B)</b><br>( <i>S. agalactiae</i> )        | 40–50 | <i>N. meningitidis</i> | 10–35 | <i>N. meningitidis</i> | 10–35 | See more often:<br><i>E. coli</i><br><i>H. influenzae</i><br><i>Pseudomonas</i> |
| <b>Listeria</b>                                           | 2–10  | <i>H. influenzae</i>   | 0–7   | <b>Listeria</b>        | 2–11  |                                                                                 |
| Staphylococci                                             | 2–5   | Streptococci           | 2–4   | Gram-negative          | 1–10  |                                                                                 |
| <i>S. pneumoniae</i>                                      | 0–5   | Gram-negative          | 1–2   | Streptococci           | 5     |                                                                                 |
| <i>H. influenzae</i>                                      | 0–3   | Staphylococci          | 1–2   | Staphylococci          | 5     |                                                                                 |
| <i>N. meningitidis</i>                                    | 0–1   | <i>Listeria</i>        | 1–2   | <i>H. influenzae</i>   | 1–3   |                                                                                 |

Remember: For the newborn and the adults > 60 yrs, empiric therapy now includes ceftriaxone, ampicillin (for *Listeria*), and vancomycin (for resistant *S. pneumoniae*). Although *Listeria* is now decreasing in > 60, guidelines still have ampicillin.

## MENINGITIS

### Bacterial Meningitis

#### Overview

Acute bacterial meningitis: If suspected, do the following CSF tests: Gram stain, C&S, cell count with differential, protein, and glucose.

Culture results are the gold standard—**unless** the patient was previously on antibiotics.

Previously, CIE (counterimmunoelectrophoresis) or latex agglutination was used, but neither is cost-effective and therefore no longer indicated for initial workups.

Overall, *S. pneumoniae* is the **most common** cause of meningitis. Next is *Neisseria meningitidis* (meningococcus). See Table 2-5. Older data showed that listerial meningitis became more prevalent again in those > 60 years old, but data published in 2011 showed that *Listeria* has actually decreased in incidence (from 20% to 4%).

The main culprit in the meningococcal group is B (**B for Bad**). There are effective vaccines against A, C, Y, and W-135, but **not** type B. (See page 2-19 for a discussion of meningococcemia.)

#### Treatment of Bacterial Meningitis

In partially treated, **gram-positive** meningitis, the bacteria stain **poorly**, and they may even appear **gram negative**!

Effective treatment of meningitis requires an antibiotic that crosses into the CSF.

Antibiotics that **easily** cross into the CSF:

- Quinolones
- Chloramphenicol
- TMP/SMX
- Metronidazole

Antibiotics that cross into the CSF **only** with **inflamed meninges**:

- PCN
- Vancomycin
- 3<sup>rd</sup> generation cephalosporins
- Aztreonam
- Imipenem
- Clindamycin

Antibiotics that either **do not cross** or **poorly cross** the blood-brain barrier:

- Erythromycin
- Tetracycline
- Aminoglycosides
- Cefoxitin
- 1<sup>st</sup> generation cephalosporins

(Note: We still use gentamicin for synergy in treating listerial meningitis even though CSF penetration is poor.)

Start empiric treatment of meningitis while the spinal fluid Gram stain and/or culture results are pending. If the lumbar puncture (LP) cannot be done immediately, start antibiotics anyway—even before the LP!

**Meningitis** in children and adults is empirically treated with **ceftriaxone or cefotaxime** (3<sup>rd</sup> generation cephalosporins) **plus** vancomycin (both for coverage of PCN-resistant *S. pneumoniae* and meningococcus). Note: Resistant *S. pneumoniae* is more likely if the patient has recently been on antibiotics. Vancomycin is used because the pneumococcus may be resistant to **all** penicillins and cephalosporins. Once your cultures grow the organism, you can narrow the treatment based on susceptibility results. (Treat PCN-susceptible strains with PCN; if PCN-resistant, use 3<sup>rd</sup> generation cephalosporin or vancomycin.)

For empiric treatment of those > 60 years **and** neonates (< 3 months), add **ampicillin** (for *Listeria*) to the above treatment. So, these patients are often started on triple-antibiotic therapy! Note that incidence of listerial



## Quick Quiz

- What organism is the most common cause of bacterial meningitis?
- What is standard empiric treatment for bacterial meningitis? For elderly and neonates?
- What labs are consistent with viral meningitis?
- *Baylisascaris* meningoencephalitis is usually caused by exposure to the infected feces of what animal?
- What is the treatment for Lyme meningitis?

meningitis in the elderly has decreased dramatically, but ampicillin is still part of the guidelines for empiric treatment in this age group.

In AIDS, ALL, or Hodgkin disease, think *Cryptococcus* and do a cryptococcal antigen. (India ink is an old test and is not used anymore.) Amebic meningitis should be the primary consideration when the meningitis patient has been swimming in **brackish** water (e.g., cow ponds).

Again, empiric treatment of meningitis: **3<sup>rd</sup> generation cephalosporin + vancomycin +/- ampicillin** (if elderly or neonate).

### Aseptic Meningitis

Viruses are the most common cause of **aseptic** meningitis—these include:

- Enteroviruses
- Mosquito-borne arboviruses (West Nile virus!) in the summer/early fall
- Mumps in the spring (Very rare today because of immunization, although there was an outbreak in Iowa in 2006.)
- HSV-2
- *Coccidioides* and *Histoplasma* (Suspect in endemic areas—arid Southwest and Mississippi/Ohio River valleys, respectively.)
- Cryptococcal meningitis (common in AIDS, Hodgkin disease, and ALL)
- Chronic **neutrophilic** meningitis—unusual (Think of *Nocardia* or fungus as possible causes.)
- Acute HIV infection (Remember in the differential of aseptic meningitis.)

Manifestations of viral meningitis:

- Headache
- Meningismus
- A nonfocal exam

CSF has lymphocytosis with usually < 250 cells/ $\mu$ L, and always < 2,000 cells/ $\mu$ L, **no** organisms, normal-to-slightly elevated protein level, and normal glucose level (~ 60% of serum glucose).

When nonbacterial meningitis is suspected, do the same CSF tests as for acute meningitis and add: fungal serology, VDRL, acid-fast smear and culture, and cryptococcal antigen test.

CSF test results that make viral meningitis **unlikely** are CSF glucose < 40% of serum glucose, CSF protein > 150 g/dL, and CSF WBC > 120 cells/mL.

Treat **cryptococcal** meningitis with IV amphotericin B + oral flucytosine (5-fluorocytosine; 5-FC), followed by oral fluconazole.

In AIDS patients, the CSF may have no WBCs with cryptococcal meningitis.

### Eosinophilic Meningoencephalitis

Eosinophilic meningoencephalitis due to *Baylisascaris*, a nematode parasite of **raccoons**, has an increasing incidence because of increased raccoon populations in suburbia, particularly in California. We discussed this briefly earlier in the Nematode topic area ([page 2-33](#)). Most infections occur in young children after they come in contact with raccoon feces in sandboxes. However, cases have also occurred in older adolescents and young adults. There is a profound eosinophilia in the CSF, and multiple granuloma form in the brain tissue. There is **no** effective treatment at this time.

Other causes of eosinophilic meningitis include *Coccidioides* and *Angiostrongylus cantonensis*.

### TB Meningitis

**Tuberculous** meningitis is sometimes manifested by cranial nerve palsies, especially of the 6<sup>th</sup> cranial nerve. Look also for “basilar” enhancement on CT scan. Other less common causes of aseptic meningitis include spirochetal infection (secondary syphilis and Lyme disease).

### Lyme Meningitis

**Lyme** meningitis can cause peripheral and cranial nerve palsies, especially of the 7<sup>th</sup> cranial nerve; so think of Lyme disease when a patient presents with Bell’s palsy and/or foot drop and a suggestive history. Treat the meningitis with ceftriaxone 2 gm qd x 21 d. Treat Bell’s palsy with oral agents alone. Alternative is high-dose PCN G.

### Spinal Epidural Abscess

Spinal epidural abscesses may be caused by either haematogenous spread or local extension (i.e., from osteomyelitis). *S. aureus* is the most common cause. Patients present with fever, spinal pain, and nerve compression problems.

Do an **MRI**. CT is not as good as MRI because it is susceptible to bony artifacts. Drainage is required. Empiric coverage should include drugs effective against staphylococci.

### Neurosyphilis

Neurosyphilis—also see more about syphilis on [page 2-24](#). CSF-VDRL test is the test of choice; it is 100% specific, but only 50% sensitive. A positive test confirms neurosyphilis, but a negative test **cannot** be used to rule out neurosyphilis. CSF FTA-ABS is very sensitive; unfortunately, it is **so** sensitive that a positive result often reflects contamination of CSF with peripheral blood, so it is **not** used. Often, treatment must be based on suspicion.

### Brain Abscess

Location of the abscess is often related to the source. Frontal lobe—think paranasal sinus: pneumococcus, *H. influenzae*, and anaerobes. Temporal or cerebellum—think middle ear: pneumococcus, *H. influenzae*, *S. aureus*, gram negative. Both frontal and parietal abscesses can be due to hematogenous spread from lung infections and endocarditis.

Diagnosis: CT scan with contrast is the **procedure of choice** (> 95% sensitivity). If accessible, aspirate the abscess and give antibiotic treatment. Occasionally, you need to surgically excise the lesion. Lumbar puncture is absolutely contraindicated if signs of increased intracranial pressure are present—such as focal neurologic signs. LP rarely helps with diagnosis anyway because the infection is not in the meningeal space. Overall, the risk of herniation is as high as 20%.

Treatment of brain abscesses is initially empiric. Pick one of the following:

- (PCN or ceftriaxone or cefotaxime) + metronidazole to cover aerobes and anaerobes.
- PCN-allergic: Give metronidazole + a 3<sup>rd</sup> generation cephalosporin.
- If you suspect *Enterobacteriaceae* (e.g., if **ear focus**), give a 3<sup>rd</sup> generation cephalosporin + metronidazole.
- If there was a history of bacteremia/endocarditis or a neurosurgical procedure, or penetrating head trauma, think *S. aureus* and add vancomycin (high incidence of MRSA). For neurosurgical patients, use ceftazidime/cefepime to cover hospital-related gram-negatives including *Pseudomonas*.

*Nocardia* pulmonary disease can spread and cause focal lesions in the brain. It is **also** a rare cause of neutrophilic aseptic meningitis (see above).

## INFECTIOUS DIARRHEA

### Overview

Fecal WBCs suggest an invasive bacterial etiology and are evident in *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *C. difficile*, and amebic GI infections. But remember: They are also seen in inflammatory bowel disease. All of these organisms can be found on C&S. So, do a **fecal WBC** and **stool C&S/O&P** if you need to work up a diarrhea. See the Gastroenterology section, Book 1, for more on diarrhea.

### Diarrhea due to *Shigella*, *Salmonella*, or *Campylobacter*

*Salmonella* is discussed on [page 2-20](#).

Note: Start cultures for *Shigella* (usually *Shigella sonnei*) as soon as possible after the bowel movement because *Shigella* dies soon after exposure to air.

Treatment: If there are fecal WBCs, do a stool C&S and O&P. However, fluoroquinolones or TMP/SMX are usually given empirically, although antibiotics may **prolong** *Salmonella* infection. Do **not** give antimotility agents for any diarrhea when there are fecal WBCs. *Campylobacter* is resistant to TMP/SMX, so give erythromycin or quinolones instead. Prolonged, intermittent diarrhea with malaise and flatus suggests **giardiasis** or *Cyclospora*.

### Diarrhea due to *E. coli*

*E. coli* is the most common cause of bacterial diarrhea (usually without blood or WBCs) worldwide, affecting both the resident children and travelers in developing countries.

There is an enterohemorrhagic *E. coli* (serotype O157:H7), which causes localized outbreaks of hemorrhagic colitis, TTP, and hemolytic uremic syndrome (HUS)—usually after eating undercooked beef or unpasteurized milk. Do **not** treat diarrhea caused by *E. coli* O157:H7 with antibiotics because you increase the risk of HUS.

Enterotoxigenic *E. coli* is the usual cause of travelers' diarrhea. Prophylaxis and treatment are discussed on [page 2-68](#).

### Diarrhea due to *Vibrio*

Vibrios—think **seafood** and **shellfish**. *V. cholerae* serogroup O1 (causes cholera) is occasionally associated with Gulf Coast crabs. The non-O1 *V. cholerae*, *V. parahaemolyticus*, and other vibrios are even more frequent causes of shellfish-associated diarrhea. These are usually self-limited. *Vibrio vulnificus* causes skin infections and sepsis, especially in the setting of immunocompromise or chronic liver disease (see [page 2-65](#)).



## Quick Quiz

- Empiric coverage for a patient with a spinal epidural abscess should cover what organism, specifically?
- Can a patient with a negative CSF VDRL still have neurosyphilis?
- What are acceptable empiric regimens for a brain abscess?
- What finding on stool evaluation suggests infectious diarrhea?
- What is a possible outcome of treating infectious diarrhea due to *E. coli* O157:H7 with antibiotics?
- *Vibrio vulnificus* can cause severe disease in which groups of patients?
- What is the current treatment of choice in patients with severe *C. difficile* diarrhea?
- What is the recommendation for treatment of recurrent *C. difficile*?
- What infection control precautions must be used on patients with *C. difficile* diarrhea?

### Diarrhea due to *C. difficile*

Antibiotic-associated **colitis** is caused by *Clostridium difficile*. (Antibiotic-associated **diarrhea** is usually just a side effect of the medicine.)

**Clindamycin, cephalosporins, and quinolones are especially likely to cause *C. difficile* disease**, but basically any antibiotic may cause it. Symptoms can occur up to **3 weeks** after the antibiotics are stopped. To diagnose, do a stool assay for the *Clostridium difficile* **cytotoxin**. A toxin assay is required because 5% of healthy persons have *C. difficile* in their stool and not all of the *C. difficile* organisms produce the cytotoxin. Community-acquired cases are becoming increasingly common.

IDSA released guidelines in 2010 with the following recommendations:

- Stop the current antibiotics.
- Treat mild-to-moderate *C. difficile* disease with metronidazole.
- Treat severe disease with **oral** vancomycin.

In severe disease with complications, give oral vancomycin (+ rectal, if ileus is present) +/- IV metronidazole. Colectomy should be considered for patients with very severe disease with rising lactate levels.

Relapses occur in ~ 1/4 of patients. Treatment is to **repeat the first regimen**—either metronidazole or vancomycin. But do not use metronidazole for more than 2 relapses. Various regimens of vancomycin and newer agents (fidaxomicin) are recommended for patients with recurrent disease.

Fecal microbiota transplantation (FMT; or fecal transplant, fecal bacteriotherapy) is a highly successful procedure for treating severe, recurrent *C. difficile* colitis and pseudomembranous colitis. Although the procedure has been around for > 50 years, it was recently “rediscovered.” Even very sick patients usually have a prompt reversal of all symptoms! Stool from a healthy donor is placed in the colon by enema or colonoscopy. The new flora flourishes and overwhelms the *C. difficile*.

Probiotics and antiperistaltic drugs are **not** recommended.

[Know.] Hand gels do **not** prevent transmission; this is important in nosocomial cases. Only hand washing prevents spread. Patients with *C. difficile* diarrhea should be isolated to a private room and placed on contact precautions.

### Diarrhea due to *Cryptosporidium*

*Cryptosporidium* is known to cause prolonged diarrhea in AIDS patients and a self-limited diarrhea in travelers. It is found with **acid-fast** stains of the stool (small, round, red organisms on a green background).

**Animals** (including humans) are the reservoirs.

### Viral Gastroenteritis

There are many viral causes of diarrhea. Rotavirus is frequently found in children. It is the most important cause of severe diarrhea in **infants** and is easily identified in their stools. Noroviruses (formerly known as Norwalk-type viruses) are associated with **clams** and **oysters**, causing “winter vomiting disease,” but it can also be **waterborne**. Identify noroviruses with the ELISA test. Look for outbreaks on cruise ships!

## SEXUALLY TRANSMITTED DISEASES

### Overview

There are many causes of STDs. Know the treatment of all STDs! Many STDs have similar manifestations consisting of genital ulcerations with regional adenopathy. (Gonorrhea does not have these.) The last treatment guidelines were released by the CDC in 2010. An update on the treatment of gonorrhea was circulated in 2011. The following discussion reflects the 2010–11 recommendations.

The U.S. Preventative Services Task Force (USPSTF) says evidence does not exist for or against screening for most STDs. CDC gives a couple of recommendations. Generally, screen populations who are “at risk.” Some established risk factors:

- Age 15–24 years
- African-American
- New partner in past 2 months
- Multiple partners
- History of previous STDs
- Drug use

- Recent exposure to jail or detention facility
- Finding sex partners from the internet
- Contact with prostitutes
- Men who have sex with men (MSM)

Screen for gonorrhea by sending an intraurethral swab specimen for Gram stain and culture or DNA probe. Alternatively, DNA amplification by PCR can be done on swab or urine.

Screen for *Chlamydia* in women (per CDC and USPSTF) in the sexually active < 25 years of age and any woman over 25 years who has the above risk factors. USPSTF has no opinion on screening men (because most are symptomatic). Screen for *Chlamydia* by sending either urine or cervical swab for DNA amplification.

Screen for syphilis in the above risk factor groups, plus during pregnancy. Order a serum RPR or VDRL.

Screen for hepatitis viruses in patients with risk factors (e.g., sexual contact and/or injection drug use). Screen for HBV by sending serum for HBsAg and anti-HBc or anti-HBs; screen for HCV by sending serum for anti-HCV.

Screen for HIV/AIDS in pregnancy and in groups with the above risk factors. Send serum for an HIV-1 antibody test (with reflex confirmatory Western blot in positive specimens). [Know.] Do **not** screen for HIV using DNA tests except in very specific circumstances, when the likelihood of a false-negative serum antibody test is high (e.g., acute infection, neonatal HIV, and in patients with indeterminate test results).

No general screening is recommended for herpes simplex infections.

### GU Infections with Genital Ulcerations

Workup of genital ulcer (or ulcers) with regional lymphadenopathy: Serologic tests for syphilis; culture or antigen test for HSV; culture for *H. ducreyi* (on chocolate agar); and, if indicated by history and physical exam, you may need to do LGV titers or biopsy the nodes to look for granulomas (Donovan bodies).

With syphilis, the ulcer is usually single, clean with raised borders, and painless. Patients with syphilis also typically have large, painless lymph nodes. (See [page 2-24](#) for more on syphilis.)

HSV presents with tender, grouped vesicles. It may or may not have regional adenopathy. Treat with oral acyclovir for the initial episode. You may also try this for severe, recurrent disease.

*Haemophilus ducreyi* causes **chancroid** in which there are **tender** genital papules, which become painful, purulent ulcers with irregular borders. There is associated,

very painful lymphadenopathy, which rapidly becomes fluctuant and ruptures. Treat with:

- 1 dose of ceftriaxone (250 mg IM),
- oral azithromycin 1.0 gm oral single dose, or
- ciprofloxacin 500 mg bid x 3 d, or
- erythromycin 500 mg tid x 7 d.

*Chlamydia trachomatis* causes lymphogranuloma venereum (LGV). It starts with a painless papule, which goes on to ulcerate and then disappears in 1–3 weeks. Inguinal adenopathy develops 2–6 weeks later. In LGV, the adenopathy may bulge over either side of the inguinal ligament, and fistulae sometime develop. Usual treatment is doxycycline 100 mg bid x 21 d. Erythromycin 500 mg tid x 21 d is effective as well.

Granuloma inguinale (“Donovanosis”) is rare. *Klebsiella granulomatis* (formerly *Calymatobacterium granulomatis*) is the causative gram-negative organism that produces terrible-looking genital ulcers, which are painless! Treat with doxycycline 100 mg bid x minimum of 21 d or until all lesions have healed.

### PID

Pelvic inflammatory disease can be caused by *N. gonorrhoeae*, *Chlamydia*, and **normal** vaginal flora (usually anaerobes). Oral contraceptives reduce the risk of severely symptomatic PID caused by gonococci, but “silent” PID has the **same** incidence of sequelae (e.g., infertility) as does that associated with peritoneal signs!

Cervical cultures are **not** reliable for PID. Occasionally, PID patients get a perihepatitis (Fitz-Hugh-Curtis syndrome) with mild LFT abnormalities; this has been caused by both *N. gonorrhoeae* and *Chlamydia*.

Because of the rate of fluoroquinolone-resistant gonorrhea, fluoroquinolones are no longer recommended.

#### Outpatient treatment for PID:

- Ceftriaxone 250 mg IM, then doxycycline 100 mg bid x 14 d +/- metronidazole 500 mg bid x 14 d; **or**
- Cefoxitin 2 gm IM and probenecid 1 gm x 1 plus doxycycline +/- metronidazole; **or**
- Other parenteral cephalosporin plus doxycycline +/- metronidazole

#### When do you hospitalize women with PID?

- Surgical emergencies cannot be excluded (appendicitis).
- Pregnancy.
- Clinical response to oral antimicrobial therapy is inadequate.
- The patient is unable to follow or tolerate an outpatient oral regimen.
- Severe illness, nausea and vomiting, or high fever are present.
- You suspect or find a tubo-ovarian abscess.



## Quick Quiz

- How do you screen for gonorrhea? For *Chlamydia*? For syphilis?
- Characterize the ulceration caused by syphilis. By chancroid?
- Discuss the clinical manifestations of LGV and granuloma inguinale.
- Know the outpatient and inpatient regimens for treatment of PID.

### Inpatient treatment for PID:

- Cefotetan 2 grams IV q 12 hours (or cefoxitin 2 gm IV q 6 hours) and doxycycline 100 mg orally or IV q 12 hours; **or**
- Clindamycin 900 mg IV q 8 hours + gentamicin.

An **alternative** to these 2 is ampicillin/sulbactam and doxycycline.

Again: When treating gonorrhea, always cover for *Chlamydia*. Tubo-ovarian abscesses require inpatient, **intravenous** antibiotic therapy—same as the inpatient PID choices above, and note that ampicillin/sulbactam + doxycycline is also recommended for tubo-ovarian abscesses.

Follow up with patients treated for chlamydial infections with a test for cure at 3 weeks. Know that the PCR test can remain positive for many weeks.

### Cervicitis

Cervicitis is usually caused by *Chlamydia* (especially if the discharge is **mucopurulent**), but also *N. gonorrhoeae*, herpes, and papillomaviruses. Because *Chlamydia* is intracellular, you must have cervical **cells** for a valid smear/culture (so scrape or use a brush). *Chlamydia* cervicitis commonly has a **mucopurulent** discharge.

### Urethritis

Urethritis—gonococcal (GC) or nongonococcal. From the 2010 CDC guidelines: Specific diagnosis of infection with *N. gonorrhoeae* can be determined by testing endocervical, vaginal, urethral (men only), or urine specimens. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of genitourinary infection with *N. gonorrhoeae*. With GC urethritis, the patient virtually always has a **purulent** discharge. The diagnosis is confirmed from either positive culture results or the finding of **gram-negative intracellular** (within PMNs) **diplococci on Gram stain** (Image 2-23).

Otherwise, consider it **non-GC** urethritis, which is usually due to *Chlamydia trachomatis* and, less frequently, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, or HSV. For 35% of cases, the cause is **unknown**.

In the non-GC urethritis, the patients usually have a **clear** urethral discharge, and a Gram stain shows WBCs and **no** bacteria. Gonococcal urethritis has a shorter incubation period (2–6 days vs. 1–4 weeks for *Chlamydia*) and produces a more **purulent** and more **productive** discharge.

In all of these patients, check a VDRL and, if negative, repeat it in 2 months (in case the syphilis was incubating when blood for the first test was drawn). Offer HIV testing to all urethritis patients.

### Treatment of urethritis [know]:

Treat **non-GC urethritis** with azithromycin 1 gm orally in a single dose or doxycycline 100 mg bid x 7 d. Azithromycin 1 gm orally x 1 dose is as effective as doxycycline and allows for observed therapy. Use azithromycin for pregnant women. Levofloxacin and ofloxacin are also effective in the non-pregnant.

**GC urethritis.** There is ~ 20% incidence of gonococcal resistance to penicillin and about the same to tetracycline. Also, because there is often a coinfection with *Chlamydia*, always cover *U. urealyticum* and *Chlamydia* with treatment of gonococcal urethritis.

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies. **Quinolone-resistant** *N. gonorrhoeae* strains are now widely disseminated throughout the United States. This emergence of resistance led the CDC to discontinue recommending any fluoroquinolone regimens for the treatment of gonorrhea in 2007.

In July 2011, the CDC released data from the Gonococcal Isolate Surveillance Project (GISP) showing that the percentage of isolates with elevated minimum inhibitory concentrations (MICs) to **cephalosporins** increased from 0.2% in 2000 to 1.4% in 2010 for cefixime and from 0.1% in 2000 to 0.3% in 2010 for ceftriaxone.

The CDC now recommends **dual** therapy for gonorrhea infections of the cervix, urethra, and rectum with a cephalosporin plus azithromycin—in hopes that routine

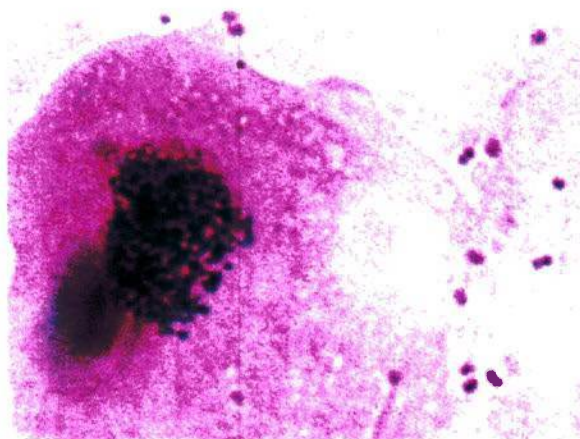


Image 2-23: Gram-negative diplococci—these are extracellular. Require intracellular for Dx

co-treatment might hinder the development of further antimicrobial-resistant *N. gonorrhoeae*.

The following is recommended for **uncomplicated** gonococcal infections of the cervix, urethra, and rectum:

ceftriaxone 250 mg IM x 1 + azithromycin 1 g PO x 1

For treatment of **uncomplicated** gonococcal infections of the **pharynx**:

ceftriaxone 250 mg IM x 1

**plus**, if *Chlamydia* has not been ruled out:

azithromycin 1 g PO x 1, or

doxycycline 100 mg PO bid x 7 days

Always think of gonococcal disease in acute pharyngitis in a sexually active adolescent!

Pregnant women: Do **not** use a quinolone or tetracycline. Use a cephalosporin for gonorrhea and either erythromycin or amoxicillin for *C. trachomatis*. If she is allergic to cephalosporins, the 2010 CDC guideline recommends azithromycin 2 gm PO x 1.

Always treat the sexual partners of patients with either type of urethritis, even if they are not symptomatic! And always treat suspected cases immediately—don't wait for C&S results!

## Gonococcemia

**Disseminated** gonorrhea: [Know!] Patients present with a fever, arthralgias, and occasionally oligoarthritis—usually of the knee or ankle. Tenosynovitis is common and is a frequent topic on Board exams. The patient typically has muscle aches and a rash with a few lesions that are papular with hemorrhage into the papules (i.e., **very red papules**). Notes: Gonococcus-associated arthritis is **asymmetric**; gonococcemia is more likely and more severe during menstruation; pili on the organism are associated with increased virulence.

Gram stain and culture have a very low yield (10%) from the lesions, but if you swab all orifices, there is an 85% yield. Even though the lesions have a low yield,

**they should still be tested** because similar lesions can be caused by other disseminated diseases, such as staph endocarditis (which **does** have a positive Gram stain and C&S).

Treat patients diagnosed with gonococcemia—including tenosynovitis—with a 3<sup>rd</sup> generation cephalosporin (ceftriaxone, ceftizoxime, or cefotaxime). Pending culture and sensitivity, single-dose azithromycin, ofloxacin/levofloxacin, or doxycycline is included to cover for *Chlamydia*.

## Epididymitis

Epididymitis is an inflammation of the epididymis—a convoluted duct on the posterior of the testicle. It is usually caused by infection [Know]:

- *Enterobacteriaceae*, especially *E. coli*, in prepubertal boys and men > 35 years of age
- STD pathogens in sexually active men < 35 years—especially *C. trachomatis*

## Vaginitis

### Bacterial Vaginosis

**Bacterial** vaginosis is a clinical syndrome resulting from the replacement of the normal H<sub>2</sub>O<sub>2</sub>-producing *Lactobacillus* in the vagina with high concentrations of anaerobic bacteria (*Mobiluncus*), *Gardnerella vaginalis*, and *Mycoplasma hominis*. There is a thin, “skim milk,” scanty, foul-smelling, non-irritating discharge that has 2 identifying features:

- 1) **Clue** cells (an epithelial cell with many adherent bacteria) (Image 2-24)
  - 2) **Fishy** odor when mixed with KOH (+ whiff/sniff test)
- There is **no cervical** discharge.

Treatment is usually **metronidazole**—oral (500 mg bid x 7 d) or vaginal gel (0.75% bid x 5 d)—or **clindamycin cream** 2% intravaginally (at bedtime x 7 d).

Alternative therapy is **clindamycin oral** (300 mg bid x 7 d) or **tinidazole oral** (2 gm daily x 2 days).

Treatment guidelines for **pregnant** women:

- Metronidazole 500 mg bid x 7 days **or**
  - Metronidazole 250 mg tid x 7 d **or**
  - Clindamycin 300 mg orally bid x 7 d
- Creams are **not** recommended in pregnancy.

The reason to treat systemically is that there is a much higher risk of preterm labor and delivery than of complications from a short course of therapy with metronidazole or clindamycin. The male sex partner does not need to be treated.

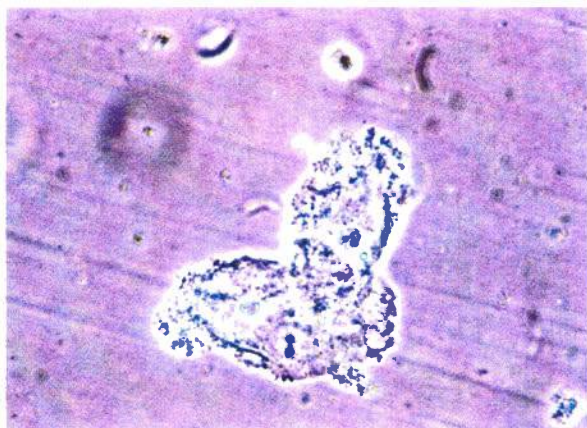


Image 2-24: Clue cells



## Quick Quiz

- What is the typical clinical presentation of disseminated gonorrhea?
- What is the best way to diagnose disseminated gonorrhea?
- Women with recurrent or recalcitrant candidal vulvovaginitis should be tested for what infection?
- Characterize the cervical specimen in a patient with trichomonas.
- What is the standard treatment for routine UTI, uncomplicated pyelo, and complicated pyelo?
- Do you treat asymptomatic bacteriuria in pregnancy?

### Vaginal Candidiasis

**Vulvovaginal** candidiasis (VVC) is usually caused by *Candida albicans*. It presents with adherent white plaques with an erythematous base. Remember that this may be a sign of undiagnosed diabetes, especially if recurrent.

Treatment:

- Uncomplicated VVC in a non-pregnant patient: butoconazole, miconazole, or terconazole vaginal creams. Oral azoles are equally effective—especially oral **fluconazole 150 mg one-time dose!**
- Treat pregnant patients with only the azole creams for 7 days.
- A subgroup of patients have **recurrent** VVC, which just does not go away and does not have an optimum treatment. Weekly topical clotrimazole and oral fluconazole 150 mg one-time dose are equally effective. Conduct **HIV testing** in women with recurrent or persistent VVC.

### Trichomonas

*Trichomonas vaginalis* infection causes a vaginitis in women, but men are usually asymptomatic. 1-week to 1-month incubation period. Trich vaginitis often presents with a profuse, thin, **frothy**, yellow-green, bad-smelling discharge (which, like bacterial vaginosis, has a positive whiff test!), vaginal erythema, and a **strawberry cervix**. Be able to identify the flagellated organism on wet mount—which is only 50% sensitive. DIF antibody staining is 70–90% sensitive. The vaginal pH is < 4.5 in the normal secretions and in yeast vaginitis. It is > 5.0 in trichomoniasis and bacterial vaginosis.

Treat trich vaginitis with metronidazole 2 grams single dose or tinidazole 2 grams single dose. Even though these are the best treatments, they are only moderately effective. If pregnant, recommendations say it is OK to give a one-time dose of 2 grams metronidazole.

### Urinary Tract Infection

Acute urethral syndrome (dysuria, frequency, and pyuria) is most commonly caused by *E. coli* and *Chlamydia trachomatis*. *S. saprophyticus* causes cystitis in young women—this is a coagulase-negative *Staphylococcus*.

The symptoms of acute urethral syndrome may be due to urethritis, vaginitis, or cystitis.

UTIs are the **most common** nosocomial infections.

In women, sexual intercourse can cause *E. coli* to be pushed up the urethra, predisposing them for an acute cystitis. Besides sexual activity, other UTI-predisposing factors in women include spermicide-diaphragm use and an inherited abnormality called Lewis non-secretor phenotype.

UTIs are rare in men and are not associated with male sexual activity, **except** in men who have sex with men. In heterosexual men, UTIs are usually a result of an abnormality in the urinary tract, such as obstruction and ureterovesical reflux from prostatic hypertrophy. Both men and women with DM, sickle cell disease, neurogenic bladders, or indwelling catheters have an increased frequency of UTIs. Also those with hyperparathyroidism or gout (secondary to stone formation and obstruction).

There is an increased frequency of **urinary tract infections** in men who have sex with men and in patients with DM, sickle cell disease, hyperparathyroidism, or gout.

Diagnosis criteria have changed. Urine cultures are no longer required on all young women with symptoms of an acute UTI. If there are no complicating factors, **pyuria alone** is an indication to treat. Renal U/S is done only in the setting of persistent fever or clinical symptoms after 48–72 hours of antibiotics.

Treatment of UTIs:

- Routine UTI: TMP/SMX for **3 days**. (TMP/SMX is more effective than amoxicillin.)
- Uncomplicated pyelonephritis: oral quinolone (levo- or ciprofloxacin) x 5–10 days; ceftriaxone or quinolone if requires IV.
- Complicated pyelonephritis: ceftriaxone, cefepime, aztreonam, or quinolone (levo- or ciprofloxacin); add expanded coverage (e.g., amp-sulbactam, ticarcillin-clavulanic acid, or piperacillin-tazobactam) if patient is immunocompromised or has urinary obstruction.

Organisms to know: *Proteus* infections are associated with stones (i.e., do a KUB to check for stones). Group B strep (*S. agalactiae*) infections are seen in pregnancy.

Pregnant women [**Know!**]: Treat **asymptomatic bacteriuria** in pregnant women (1/3 go on to pyelonephritis!), neutropenic patients, and transplant patients. Also, always admit and treat pregnant patients with pyelonephritis as a **complicated** pyelonephritis (above). Pregnancy-safe antibiotics to use for UTI/pyelonephritis



are ampicillin, cephalosporins, and TMP/SMX—but do **not** give TMP/SMX in **late** pregnancy or to early-nursing mothers because it might cause kernicterus in the child. Do **not** use tetracycline, doxycycline, **nor** quinolones.

With normal catheter care, most indwelling urinary catheters stay sterile up to 7 days. They used to be changed out after 7 days of use, but now they are changed only when the patient develops signs or symptoms of infection.

Pyelonephritis in older men is often caused by bladder outlet obstruction due to prostatic hypertrophy. Be especially on the lookout for *Enterococcus*, as well as the usual gram-negative organisms!

## OTITIS AND SINUSITIS

### Otitis

Otitis externa is also called swimmer's ear. You can easily treat this with antibiotic ear drops. Malignant (necrotizing) otitis externa involves not only the canal, but also the subcutaneous tissues and sometimes the bone. It is usually due to *Pseudomonas* infection. Suspect this in diabetics or the immunocompromised. If caught early enough, ciprofloxacin is usually sufficient treatment. If too late, long courses of parenteral antibiotics are required. If cranial nerve 7 is involved, patients need IV antibiotics and hospitalization (higher mortality rate).

### Sinusitis

Sinusitis is inflammation in the paranasal sinuses. Acute sinusitis is defined as persisting up to 4 weeks. Chronic sinusitis is defined as persisting more than 4 (some say 8) weeks. Recurrent sinusitis is 3 or more separate episodes of acute sinusitis per year.

Sinusitis is not considered "bacterial" until after 7–10 days of symptoms—viruses are usually the cause in shorter durations of symptoms.

The 2 most important factors in the development of sinusitis are patency of the ostia (blocked with thickened sinus secretions, sinus congestion, nasal polyps, and trauma) and ciliary movement (immotile cilia syndrome).

In both, the most common causative organisms are *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. Chronic sinusitis may also be caused by *S. aureus*, group A strep, *P. aeruginosa* (especially with cystic fibrosis), and anaerobes such as *Fusobacterium* and *Bacteroides*.

Fungal sinusitis is seen in patients with diabetes (especially zygomycetes), cancer, and in those receiving corticosteroid therapy. A patient with rhinocerebral zygomycosis may present with symptoms of only a sinus infection or unilateral nasal congestion. Tissue necrosis occurs as infection spreads **outside** of the sinuses with the resulting distinctive **black eschar** sometimes visible on the palate and/or nasal mucosa.

Patients with acute bacterial sinusitis have paranasal pain and pressure exacerbated by leaning forward, or they may present with maxillary teeth pain. Purulent nasal discharge with tenderness over the affected sinuses is common. They may have fever and malaise.

Note: Patients with similar headache and pressure, along with rhinorrhea and sneezing, usually have allergic or viral rhinitis—not sinusitis.

Patients with chronic sinusitis present differently, often with signs/symptoms such as chronic refractory sinus congestion, bad breath, postnasal drip, cough, and headache.

Nasal smears are most useful for differentiating allergic from bacterial sinusitis. A high number of eosinophils is seen with both allergic rhinitis **and** nonallergic rhinitis with eosinophils syndrome (NARES). Bacterial sinusitis shows large numbers of neutrophils and bacteria.

Do not do sinus cultures **except** in refractory cases; these are usually an invasive procedure. A needle is introduced via the antral nose or under the lip into the maxillary sinus; fluid is injected and then aspirated. Consider cystic fibrosis if *Pseudomonas* grows from a sinus culture (especially in a young adult with history of recurrent respiratory issues).

Radiography: Noncontrasted CT scan is the gold standard for diagnosing sinusitis. In addition to the frontal and maxillary areas, it shows the ethmoid and ostiomeatal complex. CT also shows **subtle** thickening. The T2-weighted MRI is useful for differentiating an inflammatory process (high-intensity bright) from a tumor (intermediate-intensity bright). X-rays showing opacification, air-fluid level (Waters view of the frontal and maxillary sinuses), and thickening indicate sinusitis. Today, there is **little role for regular x-rays** because of the inferior sensitivity compared to CT scan with comparable costs.

Treatment recommendations suggest waiting 7–10 days before prescribing antibiotics because the vast majority of acute sinus symptoms are not due to bacterial infection. Treat acute sinusitis with a 10–14 day course of amoxicillin or TMP/SMX. For beta-lactamase-producing strains (40% of *H. influenzae* and most of *M. catarrhalis*) or if anaerobes are suspected, use amoxicillin with clavulanic acid. Other potentially useful antibiotics are quinolones, azithromycin, and 2<sup>nd</sup>/3<sup>rd</sup> generation cephalosporins. There may be a role for intranasal corticosteroids.

Treat chronic sinusitis for a week more after symptoms resolve—at least 3–4 weeks total. Same meds can be used. Choice is often dependent on picking something different from previously used, ineffective agents.

Use endoscopic sinus surgery when medical therapy fails.

Allergic sinusitis is often treated effectively with immunotherapy with lasting benefit.

Treatment of rhinocerebral zygomycosis is emergent and aggressive—with radical surgical debridement and lipid amphotericin B. (Lipid formulation is used so that you can give higher amphi doses with less toxicity.)



## Quick Quiz

- Otitis externa in the uncontrolled diabetic is usually due to what organism?
- How many days of symptoms are required to diagnose a patient with bacterial sinusitis and prescribe antibiotics? What are the usual causative organisms?
- What are some symptoms of rhinocerebral mucor?
- How can you differentiate allergic sinusitis from bacterial?
- Treat bacterial sinusitis with which antibiotics?
- What is the clinical presentation of *M. marinum*?
- What organism is associated with osteomyelitis in a patient with sickle cell anemia (besides staph)?
- How is osteomyelitis in a prosthetic joint diagnosed?

Most other fungal meds are not effective. Posaconazole has been used successfully in conjunction with debridement; it is considered a good agent to use after patients stabilize and begin to improve on amphotericin.

## SKIN / SOFT TISSUE, BONES, JOINTS

Vibrios are found especially in shellfish. *V. vulnificus* causes large hemorrhagic bullae, followed by necrosis and lymphadenopathy +/- septicemia. Patients who are immunocompromised or have chronic liver disease are especially susceptible.

*Mycobacterium marinum* is also called “fish tank bacillus.” It causes nonhealing skin ulceration in people who work around fish tanks. Infection may present as a single granuloma, but the organism often invades the lymphatics and can cause a series of lesions over a lymph vessel similar to the lesions seen in sporotrichosis. Lesions tend to localize in the distal extremities because the organism does not grow well at body temperature. DDx: Look for acid-fast bacilli in the lesion biopsy.

Treat with ethambutol + rifampin **or** with clarithromycin + rifampin.

*Erysipelothrix rhusiopathiae* is another cause of skin infection in fishermen and meat handlers. Treat with PCN G, ampicillin, or fluoroquinolones.

**Impetigo** presents as honey-colored crusts over lesions. *S. pyogenes* is a common cause, often in combination with *S. aureus*. Remember: *S. pyogenes* also causes scarlet fever, a type of toxic shock syndrome (TSS), pharyngitis, and rheumatic heart disease.

**Osteomyelitis**—acute vs. chronic. Both have infection, but only **chronic** osteomyelitis has **necrotic bone**. Acute

is usually caused by *S. aureus*. Think *Pseudomonas* in an IV drug abuser, especially if the infection involves the vertebrae or pelvis. Think *Salmonella* in sickle cell (SS) patients.

Although less common, group B streptococci can cause osteomyelitis and prosthetic joint infections, and the incidence is rising. *Streptococcus bovis* and enterococci also cause vertebral osteomyelitis, and group G and F streptococci are seen.

Blood cultures are usually (2/3!) positive in **acute** osteomyelitis. A negative pyrophosphate bone scan **excludes** osteomyelitis, but positive scans may also be seen with other infections and with fractures. Usually, you see x-ray changes only with chronic osteomyelitis.

With sinus tract osteomyelitis, C&S of the sinus tract drainage is sufficient if you find *S. aureus*, but it is **not** sufficient otherwise—must use bone biopsy/scraping.

With suspected spinal osteomyelitis, do a needle biopsy as the 1<sup>st</sup> diagnostic procedure.

Except for **small** bone disease, you must remove the necrotic bone **before** a chronic osteomyelitis can be cured with antibiotics.

Prosthetic joints—1% get infected. Presentation is usually **chronic**. X-rays usually show bony changes, but a bone scan may be needed. (Be aware of the high rate of false positives, however.) You must perform a **joint aspiration** to determine the infecting organism. Coagulase-negative staphylococci (e.g., *S. epidermidis*) are the most common organisms recovered.

## NOSOCOMIAL INFECTIONS

Order of frequency: UTI > post-op wound infection > pneumonia.

Nosocomial pneumonia is usually **bacterial** and has the highest mortality rate of all the nosocomial infections (1/3 if bacteremic; 1/2 if gram-negative bacteremic!). It is usually caused by gram-negative organisms; next most frequently is *S. aureus*. **Resistance** may develop quickly if only a single broad-spectrum antibiotic is used. If there is an outbreak of bacterial pneumonia (or almost any illness) in the ICU, the most likely vector of transmission is the **hands** of the ICU workers.

Catheter-related infections: There are 3 types, and all 3 can cause bacteremia/fungemia:

- 1) Asymptomatic
- 2) Localized
- 3) Septic thrombophlebitis (rarest—see *Candida* on page 2-26)

Secondary **endocarditis** is more likely to occur in patients with catheters that extend **into** the heart. IV lines become infected after ~ **3 days!** Metal needles are **less** likely than plastic angiocatheters to become infected. IV catheter infections are usually due to *S. epidermidis* and *S. aureus*. Some other causes are *Candida*,

*Corynebacterium jeikeium* (especially in bone marrow transplant units), and gram-negative rods.

Treatment of catheter-related infections: Remove catheter and give antibiotic therapy for 2 weeks. Septic thrombophlebitis often requires removal of the affected vein. If there is gram-positive septicemia, start with **vancomycin** in case it is methicillin-resistant. **Exception:** If there is a gram-positive bacteremia in a patient with a Hickman<sup>®</sup> or Broviac<sup>®</sup>, you can try to treat with antibiotics for 2–4 weeks **without** removing the catheter. Again, start with vancomycin until culture results are back.

## VACCINES

### Adult Vaccinations

#### Vaccine Types

Note: Vaccines used solely in childhood are not discussed.

- Live-attenuated vaccines should **not** be given to the immunocompromised (includes pregnancy):
  - MMR
  - Varicella
  - Zoster
  - Smallpox
  - Typhoid
  - BCG
  - Yellow fever
  - Intranasal influenza (LIV)
- Killed (inactivated) are **safe** for immunocompromised:
  - Td
  - Tdap
  - HAV
  - Polio
  - Cholera
  - Rabies
  - Japanese encephalitis
  - Typhoid polysaccharide
  - HBV and HPV are recombinant
  - Pneumococcal polysaccharide (PPV)
  - Meningococcal polysaccharide and conjugate
  - Trivalent influenza (TIV)

#### Vaccine Schedules

The specific schedule for vaccinations changes very frequently. The current schedule can be found on the webpage for the Advisory Council on Immunization Practices at: <http://www.cdc.gov/vaccines/recs/schedules>.

The following is a list of vaccinations that are recommended for adults, according to age groups:

- Td or Tdap: 1 dose q 10 years. (DTaP and DT are for children < 7 years.) Tdap now approved for **all** > 7 years of age.
- HPV: 3 doses for ages 9–26.

- Varicella (chicken pox vaccine): 2 doses, if no history of infection or vaccination.
- Zoster (booster to prevent shingles): adults > 60 years.
- MMR: 2 doses if not vaccinated or 1 more if received only 1 vaccine as a child.
- Influenza: given annually to all adults. Trivalent approved for all. Live attenuated intranasal OK for those < 50 years of age.
- Pneumococcal polysaccharide: ≥ 65 years of age and at-risk individuals.
- Pneumococcal conjugate: approved by FDA for ≥ 50 years of age, but not recommended (as of publication date) by ACIP.
- HAV: at-risk adults without evidence of immunity.
- HBV: at-risk adults without evidence of immunity and no history of childhood vaccination.
- Meningococcal polysaccharide or conjugate: at-risk adults, including college freshmen and military recruits.

#### Vaccine Titers

Titer checks are recommended for these groups' post-vaccine series or booster:

**HBV:** for health care and public safety workers, patients on dialysis or with HIV/AIDS, and injection drug users. For HBV vaccine non-responders, booster vaccine will immunize 25–50%, and 44–100% of patients develop positive titers after another series of 3 shots.

Patients who do not develop measureable titers after a booster vaccine or repeat of the series are either non-responders or are already infected with HBV. The titer level should be ≥ 10 IU/mL in order to be considered adequate and protective. If the patient initially has a post-series titer of ≥ 10 IU/mL, then he is likely to be protected even if his titer subsequently falls to < 10 IU/mL over years.

#### Miscellaneous Specifics on Routine Vaccines

**Td/Tdap:** Remember there are 4 vaccine combinations for tetanus/diphtheria/pertussis: DTaP, DT, Tdap, and Td. The first two are for children < 7 years only; DTaP is the main vaccine and is given in 5 doses during childhood. DT is for kids who cannot tolerate the pertussis component. Td is the combination injection given to adults and older children as an q 10-year booster or as a booster during management of a wound. Tdap, which contains pertussis, is a newer vaccine for older children and adults. **Tdap** is now recommended to **replace** one of the q 10-year Td boosters in **all** adults regardless of age. Td is still used (for now) in managing wound infections with possible tetanus exposure. Tdap should be given in wound management, instead of Td, if the adult patient has never had a Tdap dose.



## Quick Quiz

- Which vaccines contain live virus? To which patients should they not be given?
- Which vaccines are safe to be given to immunocompromised or pregnant patients?
- Know which vaccines are recommended to adults and in what age groups.
- What should be a patient's post-HBV vaccine titer, if the vaccine was successful at inducing immunity?
- Know the recommendations for management of puncture wounds.
- How many doses of MMR are considered most desirable and protective?
- Which patient groups should be given the pneumococcal polysaccharide vaccine?
- Which patients should receive the meningococcal conjugate vaccine?
- Which patient groups should receive some form of the meningococcal vaccine?

Know the following approach to managing potential tetanus exposure. For puncture wounds or dirty wounds and the following vaccination statuses:

- Initial DTaP (or DT) series and last Td booster < 5 years ago → no vaccine necessary.
- Initial DTaP (or DT) series and last Td booster > 5 years ago → give Td (or Tdap).
- Received < 3 doses of tetanus immunizations or uncertain status → give Td (or Tdap) + tetanus immune globulin.

**Varicella** virus vaccine is recommended for all individuals  $\geq 12$  months of age who are not immune. Note that a history of chicken pox by the patient is sufficient for assuming immunity. If the adult patient doesn't know or believes he/she has had no previous infection, check immune status by lab (up to 91% are immune) before giving the vaccine. This vaccine is contraindicated in patients with immunodeficiency because it is live virus.

**Zoster** vaccine is recommended in patients  $\geq 60$  years of age, even if they have had a recent outbreak of shingles. Because it is live virus, this vaccine is contraindicated in patients with immunodeficiency or who are pregnant.

**MMR:** It is recommended that persons born after 1956 receive 2 doses of live measles vaccine. These should be given not less than 1 month apart but can be given years apart. The present recommendations are one dose at 12 months and the second dose at age 4–6 years. All young adults (since they would have been born after 1956), who have had only one live measles vaccine, should receive another.

**Pneumococcal** polysaccharide vaccine is indicated in patients with the following medical conditions, situations, and habits:

- Asthma
- Other chronic lung disease
- Cardiovascular disease
- Diabetes
- Chronic liver disease, including cirrhosis
- Chronic alcohol use
- Asplenia
- Immunocompromise (including chronic kidney disease and nephrotic syndrome)
- Cochlear implants
- CSF leaks
- Nursing home residents
- Smokers

Booster after 5 years is recommended in patients with immunodeficiencies, asplenia, and in any patient who received the first vaccine before 65 years of age.

**HAV:** Unless otherwise contraindicated, inactivated hepatitis A vaccine is universally recommended in persons  $\geq 2$  years of age.

**HBV** is universally recommended at birth and for all of those who were not immunized in childhood, particularly adolescents. Booster doses can be given q 7 years—but are not currently recommended. If the antibody level is  $\geq 10$  IU/mL, a booster dose is not needed. If a patient has been exposed to hepatitis B, has had the complete vaccination series, but the antibody level is unknown, give HBIG and a booster dose.

**Meningococcal** polysaccharide vaccine is given to at-risk adults  $\geq 56$  years of age. The **conjugate** vaccine is given to at-risk adults  $\leq 55$  years. Except for college students, patients should receive a booster vaccine after 5 years if they continue to be in a risk group (below). The vaccine is recommended for all of the following groups, with choice of vaccine based on age, as previously discussed:

- Asplenia or complement deficiencies
- First-year college students who will live in dorms; military recruits
- People who are traveling to the meningitis belt of sub-Saharan Africa
- Lab workers who work with *Neisseria*

### Unusual Vaccines for Special Situations

**Anthrax:** a nonencapsulated bacteria adjuvant vaccine for people who work with anthrax cultures or who are exposed to activities with potential for aerosolization of *B. anthracis*. This vaccine is generally limited to people who work with the organism in research.

**BCG:** Not recommended in the U.S., but commonly given to children in other countries where TB is common. BCG immunization may cause a positive tuberculin

skin test, complicating later evaluation of tuberculosis. Having received the BCG vaccine does not change the interpretation of the TB skin test in the U.S. (An indurated test should still be subjected to the same cut-offs for significance as in any other patient. See the Pulmonary Medicine section, Book 2, for discussion of TB skin testing.) Interferon-gamma releasing assays are not affected by BCG.

**Japanese encephalitis** vaccine (JE-Vax®) is recommended for travelers who plan to stay a long time in rural Asia.

**Rabies** vaccine is discussed in the section on rabies disease (page 2-40). Preexposure vaccination is recommended for those at occupational risk and travelers (and especially their children) planning extended stays in areas where dog rabies is enzootic.

**Typhoid** vaccine is recommended for travelers (> 2 years old) who go outside of the usual tourist areas within Latin America, Asia, and Africa. A newer, oral attenuated live vaccine is recommended for those > 2 years of age. It has a protection rate of 70–90%.

**Smallpox** vaccine is available on demand. Military personnel and select health care workers have been vaccinated. Contraindications to vaccination: **eczema** or household contacts with exfoliative skin conditions; immunosuppression, including from HIV and doses of corticosteroids > 20 mg/day; radiation therapy; and pregnancy.

**Polio** vaccine is not routinely recommended to persons > 18 years of age. Polio vaccine is recommended for previously unimmunized travelers to endemic areas. A booster is indicated for travelers who have had only the primary vaccination and who travel to areas where exposure to the wild-type virus is likely. Only the inactivated vaccine is recommended in the U.S.

**Yellow fever** vaccine is recommended for travel in equatorial Africa and much of tropical South America. Don't forget it is a live virus vaccine!

**Cholera** vaccine is not very effective and is rarely required.

## PROPHYLAXIS

### Meningococcemia

Meningococcemia chemoprophylaxis may be done with rifampin, ciprofloxacin, or ceftriaxone. Each is 90–95% effective in reducing nasopharyngeal carriage of *N. meningitidis*. Remember that ciprofloxacin is not routinely given to children or pregnant women (possible cartilage damage). Ceftriaxone is usually reserved for pregnant women. Note: Health care workers do not receive chemoprophylaxis unless they had recent “intimate” oral contact with the case patient ... er, like with intubation!

### Travelers' Diarrhea

Travelers' diarrhea (TD): Educate patients on what to avoid so they do not contract travelers' diarrhea in the first place. When traveling in a country where it may occur, they should:

- Not drink the local untreated water or eat ice, including mixed alcoholic drinks with ice
- Ensure the water or ice is either boiled or filtered first
- Remember that dishes are washed in local water, so drink from the can with a straw, instead of from a glass
- Avoid fresh fruits (but peeled ones are safe, like apples) and vegetables (including meat salads, like tuna), as well as condiments, such as salsas

Fancy hotels do not guarantee healthy food and water! Carbonated drinks and hot tea or coffee are usually safe.

Typically, **prophylactic** antibiotics are **not** indicated. Prophylactic antibiotics **are justified** for patients with immunodeficiencies, or severe manifestations or history of cardiac, kidney, or inflammatory bowel disease.

When given, prophylax with:

- Norfloxacin 400 mg qd
- Ciprofloxacin 500 mg qd
- Rifaximin 200 mg qd or bid
- Bismuth subsalicylate 2 tabs chewed qid

For self-treatment once travelers' diarrhea is acquired, have the patient determine the severity of diarrhea and treat accordingly. For > 4 unformed stools/day or fever, bloody, or mucopurulent stools, consider treatment with the following:

- Ciprofloxacin 500 mg bid x 1–2 days
- Norfloxacin 400 mg bid x 3 days
- Azithromycin 1,000 mg x 1 dose
- Rifaximin 200 mg tid x 3 days
- Do **not** use amoxicillin or TMP/SMX (too much resistance)

The 3-day regimens can be abbreviated to 1 day, if the diarrhea has completely ceased after a day of treatment. Loperamide can be used cautiously with the antibiotics but should not be used alone as a form of treatment.

### Malaria

Malaria prophylaxis is discussed in the section on the organisms involved (page 2-31).



## Quick Quiz

- What are the contraindications to receiving the smallpox vaccine?
- Know the recommendations for prophylaxis and treatment of travelers' diarrhea.

## FOR FURTHER READING

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